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**Deposition of Medical Aerosols in the Human Respiratory Tract: Predicting Dosages
from Nebulizers, and Deposition in the Mouth-throat using Computational Fluid
Dynamics**

by

Kevin Walter Stapleton



**A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment
of the requirements for the degree of Doctor of Philosophy**

Department of Mechanical Engineering

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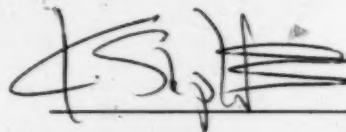
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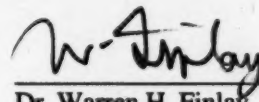
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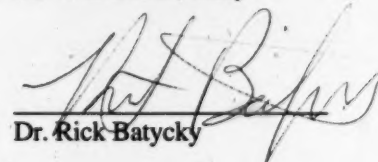
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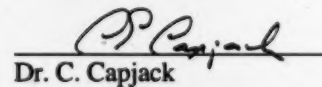
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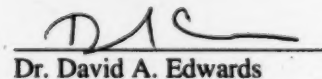
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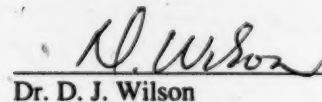
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Dedication

This thesis is dedicated to the memory of

Ms. Barbara Anne Holmes

May 21, 1956 - Jan 5, 1992

Abstract

A Lagrangian dynamical model for calculating the regional deposition of hygroscopic aerosols in the respiratory tract is presented. The model tracks a bolus of aerosol as it travels through the respiratory tract and calculates the growth of the particles using a full two-way coupled hygroscopic growth model in which the change in aerosol droplet size affects the humidity and temperature of the air in the respiratory tract. The deposition probabilities for a particle in a specific generation are calculated from theoretical and empirical expressions. A method to estimate the intersubject variability is also presented. The deposition probabilities calculated by the model agree well with available experimental data.

A methodology is presented in which experimental methods that characterize the aerosol emitted by jet nebulizers are combined with the deposition model to predict the dosage of medication delivered to the different regions of the respiratory tract. The methodology is applied to the Hudson T-Updraft II nebulizer, and the Pari LC+ nebulizer. The dosage delivered to the lungs by the Hudson is estimated as $16.1 \pm 0.5\%$ (intersubject variability 68% confidence interval: 11.8% - 20.4%) of the nominal dose put in the nebulizer, while the Pari is estimated to deliver $13.0 \pm 0.3\%$ (intersubject variability 68% confidence interval: 9.3% - 16.8%) of the nominal dose to the lung.

Computational fluid dynamics (CFD) is investigated as a tool to predict the deposition of aerosol particles in the mouth and throat by testing a commercially available CFD package (TASCFLOW3D, ASC, Waterloo, ON) on a number of geometries. For laminar

flow in tubes with simple 90-degree bends, CFD provided accurate predictions of the particle deposition. In the USP model throat, the overall filtering efficiency of the model and the deposition pattern predicted by the CFD agreed poorly with the filtering efficiency and deposition patterns determined experimentally. Finally, the code was tested in a novel geometry that approximates the extrathoracic region of the respiratory tract. Here, the deposition patterns agreed reasonably well with experimentally determined patterns, but the CFD greatly overestimated the deposition compared with experimentally determined values and the values from an empirical equation for the deposition of droplets in the extrathoracic region of the respiratory tract. The poor performance of CFD in the USP model throat and the physiologically realistic throat geometry may be due to the inadequacy of current models of turbulence and turbulent dispersion.

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Most importantly, I would like to thank all the people who have been apart of my life over the past 5+ years. You are far too many to mention, but your names, phone numbers, addresses, and notes are written in my daytimer, on my calendars, in my workbooks, and on cards, letters, and oh-so-many e-mail messages. Each and every one of you have added to my life, and in your own way, you have contributed to this work. Thank you.

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Symbols and Abbreviations

Letters

A	volume of droplets leaving the nebulizer per unit volume of air
BDF	backward differentiation
CFD	computational fluid dynamics
CT	computed tomography
C_{cor}	drag coefficient for spheres
C_f	number of photons emitted by the filter after exposure
C_m	number of photons emitted by the model after exposure
C_{p_a}	specific heat of air
C_{p_w}	specific heat of water
C_{∞}, C_K	Knudsen correction
C_R	vapour pressure reduction at the surface of a droplet due to dissolved solids (e.g. Raoult's Law for ideal solutions)
c_0	water vapour concentration at the droplet surface (g/cm^3)
$c(t)$	concentration of solute in a droplet at time t
$\bar{c}_{wall}$	the average concentration of water at the airway walls
c_w	water vapour concentration
$c_{w,in}$	water vapour concentration of air entering a nebulizer
$c_{w,out}$	water vapour concentration of air leaving a nebulizer
$(\bar{c}_{\infty}^0)_k$	the average water vapour concentration of the continuous phase in the k th generation

c_{∞}	ambient water vapour concentration (g/cm^3)
d	diameter (of particle, droplet, or airway)
D	diameter of tube
D_w	diffusion coefficient of water in air
DE	deposition fraction
DPI	dry powder inhaler
F	external forces acting on a particle
f_k	fraction of inhaled aerosol that penetrates to the k th generation
g'_k	mass transfer coefficient in the k th lung generation
GSD	geometric standard deviation
h	diffusion parameter (Equation 2.18)
h'_k	heat transfer coefficient in the k th generation
k	turbulence kinetic energy
l	turbulence length scale
l_e	average size of a turbulent eddy
L	length, latent heat of vaporization
m	mass
$\dot{m}'_{\text{wall}}$	mass transfer of water vapour from the airway walls to the air
MDI	metered dose inhaler
MMAD	mass median aerodynamic diameter
MMD	mass median diameter
MRI	magnetic resonance imaging
$O(n)$	on the order of (n)
P	statistical probability

P_n	deposition probability
$P_{n,upper}$	upper bound of the 68% confidence interval on the deposition probability
$P_{n,lower}$	lower bound of the 68% confidence interval on the deposition probability
PDA	phase Doppler anemometer
Q	volumetric flow rate
$\dot{q}'_{wall}$	heat transfer from the airway walls to the air
Q_{ci}	conductive heat transfer
Q_m	latent heat transfer
r	radius
Re	Reynolds number
RMS	root mean square
SF	scaling factor for lung model dimensions
S	stopping distance
Stk	Stokes number
t	time
T	temperature
T_ϵ	characteristic dissipation timescale
$(\bar{T}_{wall} - \bar{T}_\infty^0)_k$	difference between the average wall temperature and temperature of the continuous phase in the k th generation.
USP	United States Pharmacopeia
U	fluid velocity, fluid velocity in X-direction
u_t	friction velocity
V	volume
V_{dead}	instrumental dead space

V_0	initial volume of liquid in the nebulizer
v_f	fluid velocity
v'_f	instantaneous velocity of a turbulent eddy
v_p	particle velocity
v_s	settling velocity
V_T	tidal volume
W	volume of water vapor leaving the nebulizer per unit volume of air
x_h	hydrodynamic entrance length
x_i^o	old particle position
x_i^n	new particle position
y^*	dimensionless distance from the wall

Subscripts

A	alveolar region of the respiratory tract
ae	aerodynamic
a, air	air
E	extrathoracic region of the respiratory tract
f	fluid
i	value at a particle surface
k	lung generation
l	liquid
o	initial value
p	particle
s	solid

<i>TB</i>	tracheobronchial region of the respiratory tract
<i>v</i>	vapour
<i>wall</i>	value at the wall

Superscripts

<i>hold</i>	inspiratory pause in the breathing cycle
<i>in</i>	inhalation portion of the breathing cycle
<i>n</i>	value at the new timestep
<i>o</i>	value at the old timestep
<i>out</i>	exhalation portion of the breathing cycle

Greek symbols

α	bifurcation angle
β	angle with horizontal (Equation 2.16)
$(\Delta c_w^0)_k$	the change in water vapour concentration between the beginning and end of the <i>k</i> th generation when no droplets are present
Δm_{neb}	change in total mass of a nebulizer
Δt_k	average residence time of a particle in a generation
$(\Delta T_w^0)_k$	temperature change in the continuous phase between the proximal and distal ends of the <i>k</i> th generation
δt	timestep for integration of particle trajectories
ϵ	sedimentation parameter (Equation 2.15), and turbulence dissipation
ϕ	ventilated fraction
η	filtering efficiency

κ_a	thermal conductivity of air
ρ	density
$(\bar{\rho}_{air}^0)_k$	average density of air in the k th generation
$\sigma_{n, norm}$	normalized standard deviation
τ_e	eddy lifetime
τ_w	wall shear stress
μ	dynamic viscosity
ν	kinematic viscosity
ψ	fraction of inhaled air passing through the mouth
∞	ambient, at infinity

1. Introduction

Aerosols are airborne suspensions of particulate matter, and are a natural component of our environment. The troposphere, i.e. the lowest 10 km or so of the atmosphere, contains between 10^2 and 10^6 particles per milliliter, most of which fall into the size range of 0.01-1.0 μm (Morrow, 1974). These particles are inhaled during normal respiration, and may be deposited in the respiratory tract by coming into contact with the surface of the airways. The deposition of inhaled particles has a probability that depends on the aerodynamic and thermodynamic properties of the particles, the morphology of the respiratory tract, and the airflow and mixing behavior in the airways. Inhaled particles may include toxic agents whose deposition in the respiratory tract may have adverse effects on the body. For this reason, predicting the deposition of these particles in the respiratory tract has attracted considerable interest.

The respiratory tract has elaborate defenses against particles that occur naturally in the atmosphere. The morphology and fluid mechanics of the respiratory tract have evolved so those particles in the size range most prevalent in the atmosphere (i.e. particles with diameters on the order of a few tenths of micrometers) have the least chance of depositing. Particles with diameters on the order of a few micrometers tend to deposit in

the conducting airways and are removed by the muco-ciliary transport system over a number of hours. Larger particles tend to deposit in the mouth and pharynx, and are quickly removed by coughing through the mouth, or swallowing and being passed through the digestive tract. Particles smaller than about $0.01\ \mu\text{m}$ have quite high probabilities of depositing in the lungs, but do not occur frequently in the natural atmosphere and do not carry much mass, so their toxicological effects are usually minimal.

Industrial society has significantly changed the aerosols found in the atmosphere. Many of these aerosols are toxic, and are of different sizes than those seen naturally in the atmosphere, so the body is ill equipped to defend against them. This leads to the possibility of inhaled particles depositing in the respiratory tract and damaging the delicate tissues in the lungs thereby impairing its effectiveness, and of toxic chemicals gaining easy access to the circulatory system and being spread throughout the body.

These concerns have generated considerable interest in being able to predict the deposition of aerosols in the respiratory tract, with the goal of predicting the effects of human exposure to hazardous environments. Techniques have been developed to study the deposition of aerosols in the respiratory tract *in vivo*, and empirical models have been developed. Concurrently, research on aerosol behavior has lead to a greater understanding of the physics of aerosol deposition in the respiratory tract, and to the development of deposition models based on the theoretical expressions for the deposition of aerosol particles in tubes. The structure and functionality of the respiratory tract is an important feature of these deposition models, and their development has encouraged an

improved understanding of the morphology, fluid dynamics, and functionality of the human respiratory tract.

In the past century, aerosolized drugs (therapeutic aerosols) have been used to treat respiratory tract diseases and are the preferred means of delivering some medications (c.f. Williams, 1974). However, the performance and efficiency of devices used for producing therapeutic aerosols differ greatly, and it has been suggested that unsatisfactory clinical results may be due in part to the improper selection and operation of this equipment (Newman *et al.* 1986). Procedures which allow estimation of delivered dosages from these devices are useful in improving the device design and delivery protocols for therapeutic aerosols, and many of the techniques used to study the deposition of hazardous aerosols in the respiratory tract have been applied to the deposition of therapeutic aerosols to improve the efficiency and efficacy of aerosol therapy.

There are three types of devices that are commonly used for producing and delivering therapeutic aerosols. Nebulizers produce aerosol from a drug formulated as a solution, or as a suspension, using conventional air-water spray atomization technology. Metered dose inhalers (MDIs) contain a pressurized cylinder with drug, propellant, and excipients. Actuating the MDI results in a spray containing a precisely metered dose of the medication being released from the canister. MDIs are inexpensive and convenient, but are inefficient when not used correctly. In a dry powder inhaler (DPI), the drug is formulated as a powder, and the device is similar in size, cost and convenience to an MDI. However, for effective deposition in the lungs, DPIs require a minimum inhalation

flow rate that small children or patients with severe respiratory distress may not be able to accomplish.

Studies comparing the performance of these devices have often sided with MDIs because of their relatively good performance, convenience, and low cost. However, caution should be used when applying these results in general, since some of the devices used in these studies are much less efficient than newer devices (Finlay *et al.* 1997a).

Reviews of aerosol therapy techniques and devices (e.g. Consensus Conference on Aerosol Delivery, 1991) discuss the advantages and disadvantages of each device type, and identify specific areas where each device type is most effectively used. Nebulizers excel at delivering large doses of medications to the lung (e.g. 15-20 mg/hr), and delivering medication over long periods of time during tidal breathing.

This manuscript addresses many of the issues surrounding the deposition of therapeutic aerosols in the respiratory tract, and in evaluating the performance of nebulizers. Issues involved in the performance and deposition from MDIs and DPIs is an area of ongoing research, although many results are available in the archival literature, and the reader is referred there for details.

Two dimensional (2-D) gamma scintigraphy is used in many clinical investigations of nebulizer deposition to estimate the amount of aerosol deposited in the extrathoracic, central, and peripheral regions of the lungs (Matthys & Köhler 1985, Johnson *et al.* 1989, Ilowite *et al.* 1991). These *in vivo* studies show a marked difference in the total deposition and the deposition pattern of a specific drug delivered by different nebulizers, and a specific nebulizer delivering different drugs. This indicates that

different drugs may need to be tested with each nebulizer to determine the most effective combination.

Difficulties in determining regional deposition using 2-D gamma scintigraphy have been discussed by Trajan *et al.* (1984). In particular, the three dimensional (3-D) structure of the lung is collapsed onto a 2-D image, making it difficult to estimate the true 3-D distribution of the aerosol. Single photon emission computed tomography (SPECT) provides 3-D images of the lung, and improved estimates of the ratio of aerosol deposited in the peripheral vs. central regions of the lung (Logus *et al.* 1984, Phipps *et al.* 1989), but the cost, complexity, and duration of the procedure limits its use (Logus *et al.* 1984). In addition, difficulties in determining gamma ray attenuation makes absolute dosage estimation difficult, limiting the results supplied by many researchers to relative dosage distribution estimates (e.g. penetration index).

Another method of investigating nebulizer performance, which is often used to compare different delivery systems (e.g. nebulizers vs. MDIs), is to consider the clinical effect of the delivered medication on respiratory system performance, often characterized by FEV₁ (Zainudin *et al.* 1990, Blake *et al.* 1992). This methodology provides physicians with estimates of how much medication to prescribe to their patients, but can not parametrically characterize the performance of the devices in detail, or provide a measure of the distribution of the medication in the respiratory tract.

As an alternative to costly and time-consuming clinical measurements, nebulizers are often characterized on the bench by collecting the aerosol on filters. These studies provide some information on the efficiency of the aerosol generation capabilities of the nebulizer, but they do not include any information on the inhalability of the aerosol, and

its probable sites of deposition in the respiratory tract. Most often, this information is combined with a characteristic description of the produced aerosol, usually in the form of a 'respirable fraction'. The respirable fraction is loosely defined as the percentage of the aerosol (by mass) contained in particles between 1 μ m and 5 μ m (or between 1 μ m and 6 μ m, or some other definition, depending on the author) which is generally viewed as the particle size range with the highest probability of deposition in the lungs. However, Finlay *et al.* (1997b) have shown that respirable mass is not a useful measure of nebulizer performance for many aerosol sizes.

This manuscript presents a different approach to the evaluation of nebulizer performance. A deposition model based on theoretical expressions for the deposition of aerosol particles in a model of the respiratory tract is used to predict the deposition patterns of the aerosol output by the nebulizer. Part 2 discusses the development of this model. Part 3 describes how the output of a nebulizer can be measured so it can be combined with the deposition model to produce regional dosage estimates as a method of evaluating nebulizer performance.

The downfall of these current evaluation methods is that at best they can predict regional deposition patterns, i.e. they do not address the local sites of deposition in the airways. For example, for mouth breathing, only one dosage or deposition probability is given for extrathoracic deposition, and there is no indication of the amount of aerosol deposited on the tongue vs. the larynx. In addition, while the predicted deposition is in reasonable agreement with population averages, these methods are not able to predict the deposition in individual subjects.

One technique that can overcome the previously mentioned deficiencies is computational fluid dynamics (CFD). CFD uses computers to solve the mathematical equations that describe fluid flow and particle motion, and may be able to be used to study the airflow and particle deposition in the respiratory tract. However, the airflow in the respiratory tract is complex, and accurate results may not be achievable under certain circumstances with current CFD technology. Part 4 of this manuscript discusses some issues that must be considered when using CFD techniques in the respiratory tract, and compares results of simulations of particle deposition in a model of the extrathoracic region to experimental data.

2. Deposition Modeling

2.1 Overview

A deposition model is a series of equations that predict the probability that a particle will deposit in the respiratory tract. There are a number of different types of deposition models described in the literature, and it is useful to define the descriptive terms used in this thesis. Here, we divide deposition models into two major categories: empirical models, and dynamical models. Empirical models consist of equations based solely on empirical curve fitting of data, and consist of models in which the equations are fit to experimental data, as well as models where the equations are fit to other data. (For example, the empirical model of Rudolf *et al.* (1990) duplicates the results of the Eulerian dynamical model of Egan & Nixon (1985)). Dynamical models are based on the dynamics of fluid flow and particle motion in the respiratory tract and are differentiated by the frame of reference used to describe the motion: an Eulerian model uses a fixed reference frame, while a Lagrangian model follows an aerosol bolus as it travels through the lung. Here, we discuss the development of a Lagrangian dynamical model.

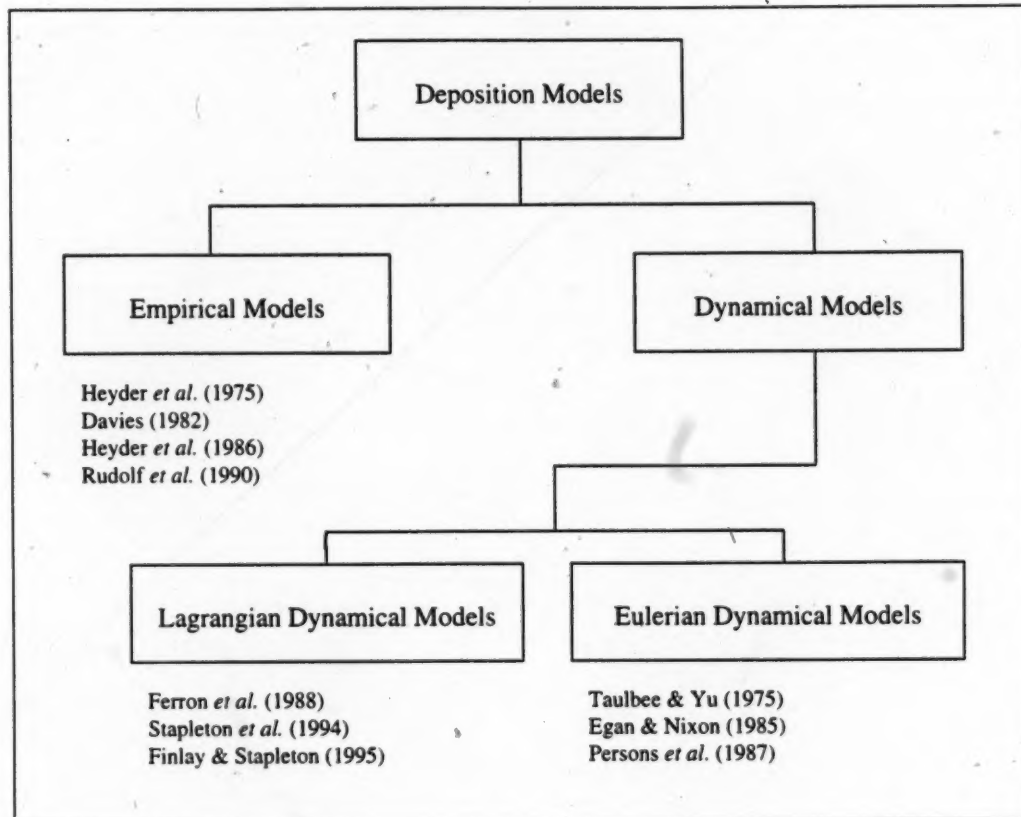


Figure 2.1: Classifications of deposition models

During breathing, air passes through different anatomical regions of the respiratory tract. Particles that do not deposit in the first region are passed to the second region, where they may deposit, or be passed on to the next region. It is therefore convenient to think of the different regions of the respiratory tract as filters, and equations can be written which describe the filtering capabilities of the region. On inhalation, aerosol passes in through the filters, each filter removing a percentage of the suspended particles. On exhalation, the aerosol passes back out through the same filters before exiting the respiratory tract.

The equations describing the filtering efficiency or deposition probability (the terms are used interchangeably here) in empirical deposition models typically depend only on the particle size, the tidal volume, and breathing frequency. Heyder *et al.* (1975) and Davies (1982) present empirical models for the total deposition of aerosol particles in the respiratory tract. Both models have only one equation, and therefore would correspond to having one filter representing the entire respiratory tract.

A multi-filter empirical model is presented by Heyder *et al.* (1986), which can predict aerosol deposition in the extrathoracic, bronchial, and alveolar regions. The deposition in the extrathoracic region, DE_E , is given by:

$$DE_E = \eta_E \phi_E \quad (2.1)$$

where η_E is an empirical expression for the deposition probability in the extrathoracic region, and ϕ_E is the fraction of the tidal volume that passes entirely through the extrathoracic region. The deposition in the tracheobronchial region, DE_{TB} , is given by:

$$DE_{TB} = (1 - \eta_E) \eta_{TB} \phi_{TB} \quad (2.2)$$

where η_{TB} is an empirical expression for the deposition probability in the tracheobronchial region, $(1 - \eta_E)$ represents the fraction of the initially inhaled aerosol which is available for deposition in the tracheobronchial region, and ϕ_{TB} is the fraction of the tidal volume that passes entirely through the tracheobronchial region.

Lagrangian dynamical deposition models are similar in concept, but may have more filters. The model described in this thesis has 51 filters, one filter for each generation of the lung model on inhalation and exhalation, and the deposition in filter k is given by:

$$DE_k = \left(\prod_{i=0}^{k-1} (1 - \eta_i) \right) \eta_k \phi_k \quad (2.3)$$

The difference between empirical and dynamical deposition models is the form of the equations for the deposition probabilities, η_k . In empirical models, the deposition probabilities are based on empirical fits to experimental data. In Lagrangian dynamical models, these equations are based on the physics of particle transport through an idealized lung model.

Lagrangian dynamical deposition models are based on the work of Findeisen (1935) who studied the deposition of NaCl aerosols in animal lungs, and recognized that aerosol deposition in the lungs was governed by the same physical laws that govern aerosol behavior in the atmosphere. By combining these laws with a simplified lung model, Findeisen was able to develop the first particle deposition model for humans.

Recent improvements in aerosol deposition modeling have occurred due to improved morphometric descriptions of the lungs, and a better understanding of aerosol behavior in systems of bifurcating tubes. Many of these improvements were spurred on by the development of improved *in vivo* imaging techniques, and a better understanding of *in vivo* aerosol deposition.

Structural differences between deposition models are reviewed in detail Heyder, & Rudolf (1984) for deposition models published before 1984. Heyder & Rudolf identify three "primary deposition models", or "formalisms" upon which all others are based. The first primary deposition model was presented by Findeisen (1935), and is characterized by treating the respiratory tract as a system of discrete morphometric regions. Particles are removed from the air flowing through these regions by gravitational, inertial, and

diffusional forces. Breathing is approximated as a pattern of constant flow with adjustable periods of inhalation and exhalation. This type of model lends itself to empirical and Lagrangian dynamical deposition models and the description of a deposition model as a series of filters. The second primary deposition model identified by Heyder & Rudolf was presented by Altshuler (1959). Here, the respiratory tract is treated as a spatially continuous filter, but the breathing pattern is treated similarly to Findeisen primary deposition models. This formalism is rarely used. The third primary deposition model identified by Heyder & Rudolf was first presented by Taulbee & Yu (1975), although Pack *et al.* (1972) present a similar gas transport model which was later modified into a deposition model by Egan & Nixon (1985). Here, the respiratory tract is approximated by a channel with a variable cross-section along its one-dimensional length, and breathing is accounted for in the boundary conditions for the gas and aerosol transport equations. This formalism lends itself to Eulerian dynamical models. Since 1984, a model based on the Taulbee & Yu formalism has been presented by Persons *et al.* (1987), and models based on the Findeisen formalism have been presented by Ferron *et al.* (1988a, 1988b), the ICRP (1994), as well as the model presented here.

The following section describes the development of our Lagrangian dynamical regional deposition model. This thesis is not intended to be a comprehensive review of all aspects of pulmonary function and deposition modeling, and only deals with subjects directly involved in the development and use of our model.

2.2 Morphology and models of the human respiratory tract

2.2.1 Respiratory tract morphology

The human respiratory tract consists of the lungs and a series of passageways through which air is passed through the body to the lungs. Early studies of the structure of the lungs focused on the anatomical features, and it wasn't until the work of Findeisen (1935), and D'Arcy Thompson (1942) that modern engineering principles were applied to the flow of air in the body.

Thompson (1942) showed that biological systems obey the 'principle of similitude', that is, they do not violate basic physical laws in their development. Thompson showed that the asymmetrical dichotomous branching pattern seen in the lungs is consistent with the concepts of minimal energy loss and minimum volume. Indeed the lungs are a remarkable organ in that they provide a surface area of approximately 150 m^2 for gas exchange between the atmosphere and the blood stream in a volume of between 5 and 6 liters.

One of the first comprehensive morphological studies of the lungs was done by Weibel (1963). In his classic monograph, Weibel studied casts of 5 subjects, and presented average values for the dimensions of each generation of the bronchial tree. Dimensions for the first 10 generations were obtained by direct measurement of lung casts. To estimate the total number of bifurcation generations, Weibel dissected the lungs and studied the acini in detail (an acini is the largest structure in the lungs which contains only respiratory elements, i.e., it contains respiratory bronchioles, alveolar ducts and sacs distal to a single terminal bronchiole). Weibel concluded that most acini were composed

of three generations of alveolar ducts (i.e. ducts completely covered with alveoli), and three generations of transitional bronchi (i.e. ducts partially covered with alveoli). By estimating the number of alveoli on each tube in the acini, and the total number of alveoli in the lung, Weibel calculated that the lungs contained a total of 23 generations of homogeneous dichotomous branching.

Weibel presented his findings as two models; the most widely used of which is the Weibel 'A' model (Weibel 1963). The Weibel 'A' model assumes that the lungs are a network of cylindrical tubes which branch in a regular dichotomous fashion. The lengths and diameters of the first 10 generations are given by the average values from the cast measurements. Weibel's least squares gives the length of a tube in generation k as:

$$L_k(k) = L_0 \cdot e^{-0.92k} \quad (2.4)$$

for $0 \leq k \leq 3$ and $L_0 = 12$ cm, and

$$L_k(k) = L'_0 \cdot e^{-0.17k} \quad (2.5)$$

for $4 \leq k \leq 10$ and $L'_0 = 2.5$ cm, and the diameters as:

$$d(k) = d_0 \cdot 2^{-k/3} \quad (2.6)$$

for $0 \leq k \leq 10$ and $d_0 = 1.2$ cm. It is interesting to note that these functions are consistent with the concept of minimum energy loss (or minimum entropy gain) and minimum space for a network of tubes with a regular dichotomous branching pattern (Thompson 1942, Horsfield & Cumming 1967, Glansdorff & Prigogine 1971). Weibel found that the length and diameter of the terminal bronchiole leading into the acinus was consistent with it being generation 16 in his numbering scheme, and used Equations (2.5) and (2.6) to predict the length and diameters of the remaining conducting (or tracheobronchial) airways. The lengths and diameters of the tubes in the alveolar region (generations 17-

Generation	Length (cm)	Diameter (cm)	Cumulative volume (cm ³)
0	10.26	1.539	19.07
1	4.070	1.043	25.64
2	1.624	0.710	28.64
3	0.650	0.479	29.50
4	1.086	0.385	31.70
5	0.915	0.299	33.76
6	0.769	0.239	35.95
7	0.650	0.197	38.39
8	0.547	0.159	41.14
9	0.462	0.132	44.39
10	0.393	0.111	48.26
11	0.333	0.093	53.01
12	0.282	0.081	59.14
13	0.231	0.070	66.26
14	0.197	0.063	77.14
15	0.171	0.056	90.70
16	0.141	0.051	109.26
17	0.121	0.046	139.32
18	0.100	0.043	190.61
19	0.085	0.040	288.17
20	0.071	0.038	512.95
21	0.060	0.037	925.25
22	0.050	0.035	1694.17
23	0.043	0.035	3000.00

Table 2.1. The dimensions of the Weibel 'A' model scaled to 3000 cm³.

23) are not predicted well by these equations, and Weibel instead used average values from direct measurements of these airways. It should be noted that Weibel measured every generation in each cast up to generation 10, but only a representative sample of the more distal airways.

The Weibel 'A' model is not an accurate description of the respiratory tract for a number of reasons. First, and most obvious, the Weibel 'A' model assumes symmetrical dichotomous branching, whereas the airways in the human lung undergo asymmetric dichotomous branching. Secondly, because of the regular branching pattern, the model overpredicts the number of alveolar airways. However, symmetry and simplicity make it popular for modeling the geometry of the lungs.

The total volume of the Weibel 'A' model is 4800 cm³, which corresponds to approximately 75% of the functional residual volume (FRC) of an adult male (Weibel, 1964). Tidal breathing occurs at approximately 50% FRC, so the dimensions given by Weibel (1963) should be scaled when calculating deposition during tidal breathing.

Hughes *et al.* (1972) studied the effect of lung inflation on the dimensions of the airways in dogs and found that on average, they scaled with the cube root of the lung volume. A scaling factor, *SF*, can be calculated by:

$$SF = \sqrt[3]{\frac{3000}{4800}} = 0.86 \quad (2.7)$$

which when multiplied by the length and diameters of the airways will scale the model to 3 liters.

Hansen and Ampaya (1975) studied the morphology of the acini and proposed modifications to the Weibel 'A' model to overcome some of its shortcomings. They found that the respiratory bronchiolar and alveolar ductural cross-sectional area, and alveolar surface area increased more rapidly with generation than predicted by the Weibel 'A' model, and proposed a model based on their data, and Weibel's data for generations 0-10. Their model has fewer small bronchi and respiratory bronchi (generations 11-20), and has more alveolar ducts than the Weibel 'A' model.

Olson *et al.* (1970) considered the average geometrical parameters of the respiratory tract as well as a 'consideration of the series-parallel arrangement' of the airways in the lungs. They combined data from different lung morphology studies with their own observations of lung function and presented an asymmetric model which closely resembles the Weibel 'A' model, but has fewer airways at higher generations.

Yeh & Schum (1980) took a different approach and considered 'pathways' to alveolar sacs instead of generations of tubes. This focus allows them to consider both asymmetry of the branching structure, and portions of the lungs (e.g. one lobe). Their geometry is derived from measurements of casts, and the branching structure is very similar to Weibel.

Haefeli-Bleuer & Weibel (1988) studied the morphology of the acinus in detail using lung casts, and found that intraacinar airways branch dichotomously over 6-12 generations, with an average of 9 interacinar generations. With their measured acinar volume of 187 mm^3 , they calculated that the entrance to the acinii is at generation 14, a location consistent with the measured length and diameter of the terminal bronchiole as predicted by Equations 2.5 and 2.6. The modifications they propose to the Weibel 'A' model are limited to the length and diameter of generations 15-23, and a change in the location of the start of the alveolar region to the 15th generation.

With this variety of lung models, it is not obvious which is best to use with a deposition model. This issue was addressed by Yu and Diu (1982a) and Martonen (1983), who studied how different lung models would affect the deposition predicted by a mathematical deposition model. Both studies showed that the standard Weibel 'A' model, scaled to 3 liters, gave deposition probabilities which most closely approximated the population average results from experimental studies, and in spite of its morphometrical inaccuracies, it was suitable for use in deposition modeling studies. The deposition model described in this thesis uses a Weibel 'A' model scaled to 3 liters.

All of the above models assume that the lung is a series of cylindrical tubes, and there is no description of how the tubes are joined. This is an important question for

researchers studying the fluid flow in the airways, and the deposition of particles within the bifurcation. Olson (1972) studied the airflow through models of bifurcations obtained by averaging the geometry from over 500 bifurcations in lung casts. Olson (1972) describes the proximal 80% of the parent tube as being cylindrical. The last 20% of the parent airway is a transition zone to the daughter tubes. The cross section becomes more elliptical, while maintaining a constant cross-sectional area. When the minor axis of the ellipse is approximately equal to the radius of the daughter tube, the shape flattens, and the cross-sectional area increases until the carina bisects the tube, and forms the two daughter tubes. The carina is described as a curved wedge, with the radius of curvature proportional to the radii of the daughter tubes.

Heistracher & Hofmann (1995) noted that many researchers studying the flow through airway bifurcations do not specify how the transition region is modeled, and propose a bifurcation model similar to Olson (1972), with slight differences in the radii of curvature of the carina and transition zone.

The shape and size of the mouth, pharynx, larynx, and upper part of the trachea, which comprise the extrathoracic airways of the respiratory tract, are not as well defined, or modeled, as the lower airways. Many researchers creating computer models to predict aerosol deposition in the respiratory tract avoid this problem by using an empirical equation to predict deposition in the extrathoracic region, and thereby avoid any description of the extrathoracic airways.

The geometry of the upper airways has been studied by researchers in diverse fields. One such field is sleep disorder research, where craniofacial and pharyngeal morphology are the main contributors to obstructive sleep apnea (OSA) syndrome (c.f.

Lowe 1990). Lowe & Fleetham (1991) and Pae *et al.* (1994) provide the average locations of most anatomical features of the mouth and pharynx in the middle sagittal plane from CT scans of about 35 normal subjects (c.f. Figure 3.1). Rodenstein *et al.* (1990) study the transverse shape of the pharynx, and show that the pharynx is an elliptical cylinder, with the ratio of the major and minor axes dependent on whether the subject is normal, a simple snorer, or a patient with OSA.

Baer *et al.* (1991) used magnetic resonance imaging (MRI) techniques to measure the shape of the vocal tract superior to the glottis. Unfortunately, the measurements were done while the patient was producing vowel sounds, so the data has limited applicability to simple tidal breathing. Sorokin (1992) developed a mathematical model for predicting the shape of the mouth and pharynx, but again the model is focused on the shape of the airway during the production of speech.

The shape and mechanical properties of the larynx and vocal cords were studied and modeled by Titze (1973) and modified by Titze (1989). These models provide a detailed description of the morphology of the vocal cords and the larynx, although they ignore the false vocal cords which were included in the model of Miller *et al.* (1989). Scherer & Titze (1983) studied the fluid flow through models of the larynx, and describe a realistic model consistent with the other studies. The movement of the vocal cords during tidal breathing was studied by Stanescu *et al.* (1972) and Brancatisano *et al.* (1983) who measured the variation in glottal width with time.

The above-cited literature is used to construct an idealized model of the extrathoracic airways suitable for study with computational fluid dynamics techniques. Details of the model are given in Section 4.2.

2.2.2 Heat and vapour transport models

Inspired air needs to be conditioned to 37°C and 99.5% RH before it reaches the alveoli to ensure normal functioning of the lungs. This conditioning normally requires heat and vapour transport from the walls of the airways to the inspired air. Cole (1953) and Cranston *et al.* (1954) performed some of the initial thermal mapping of the airways, and this information was added to by many researchers up to and including McFadden *et al.* (1985) who used a thermal probe to study the temperature and relative humidities *in vivo* at different flow rates.

A number of models describing the heat and vapour transport between the walls of the respiratory tract and the inspired air have been published (Saidel *et al.* 1983, Ferron *et al.* 1985a, Hanna & Scherer 1985, Ingenito *et al.* 1986, Ferron *et al.* 1988a, Tsu *et al.* 1988, Daviskas *et al.* 1990). Tsu *et al.* (1988) performed a control volume analysis on the airways, and present a sophisticated model which can predict airway wall conditions as well as air temperature and relative humidity. Daviskas *et al.* (1990) present a model well suited for integration with a deposition model. Their model is based on an analytical solution to the heat transport equation in a cylindrical tube. The equations for the bulk temperature and water vapour concentrations are relatively simple, and do not require the computational expense of the other models (Daviskas *et al.* 1990). The temperature and humidity profiles predicted by this model are shown in Figures 2.2 and 2.3.

Eisner *et al.* (1990) and Graham & Eisner (1990) present a model of heat and vapour transport from the airway walls that includes the effects of inhaled aqueous aerosols. However, Eisner *et al.* (1990) and Graham & Eisner (1990) neglect momentum diffusion but include radial thermal and mass diffusion. This is not consistent, since the

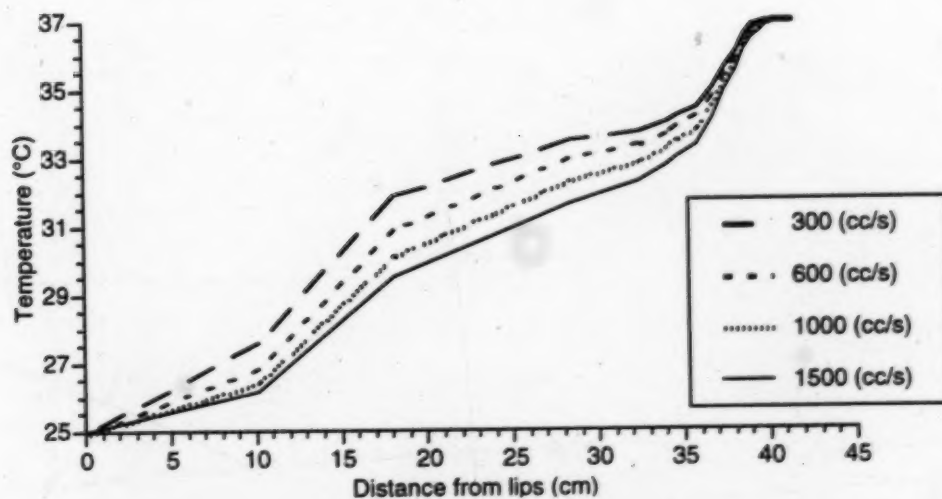


Figure 2.2. The mean end of inhalation temperature of the respiratory tract for inhalation flow rates representative of tidal breathing (300 cm³/s) through single breath inhalation maneuvers (1500 cm³/s) for a Weibel 'A' lung scaled to 3000 cm³. Data from Daviskas *et al.* (1990).

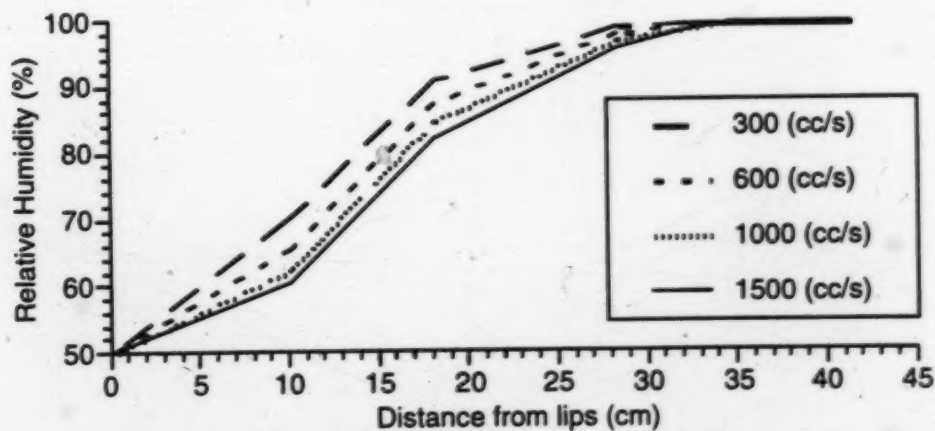


Figure 2.3. The mean end of inhalation relative humidity of the respiratory tract for inhalation flow rates representative of tidal breathing (300 cm³/s) through single breath inhalation maneuvers (1500 cm³/s) for a Weibel 'A' lung scaled to 3000 cm³. Data from Daviskas *et al.* (1990).

Prandtl number (which is the ratio of thermal diffusion to momentum diffusion) and the Schmidt number (which is the ratio of mass diffusion to momentum diffusion) are both of $O(1)$ for typical air/water vapour mixtures encountered in the respiratory tract.

2.3 Respiratory tract fluid dynamics

The ability of a flow to carry particles is partially influenced by the flow regime of the carrier fluid, and it is therefore useful to review the flow regimes in the respiratory tract. General reviews have been presented by Pedley (1977), Swift & Proctor (1977), Chang & Menon (1993), and Shadle (1996) among others.

During normal tidal breathing, flow rate through the extrathoracic regions is approximately $300 \text{ cm}^3/\text{s}$. The Reynolds number for this flow is approximately 1200, lower than the transition value of about 2300 for smooth, straight, circular tubes. However, separation from complex shapes and rough surfaces may produce turbulence, so it is unclear whether the airflow in the airways superior to the glottis during tidal breathing is completely laminar. Forced inhalation maneuvers can cause flow rates more than 10 times those seen in tidal breathing, resulting in Reynolds numbers of over 10,000; so turbulence is expected in these flows.

Dekker (1961) studied the transition between laminar and turbulent flow in plastic casts of the larynx, trachea and main bronchi. By injecting a dye stream into water flowing through these casts, Dekker found that "instabilities" developed at flow rates equivalent to $72 \text{ cm}^3/\text{s}$. At flow rates equivalent to $116 \text{ cm}^3/\text{s}$, Dekker found that the flow in the trachea became turbulent, and that the turbulence was still present in the main bronchi.

Early measurements of the flow characteristics in the extrathoracic airways focused on determining the relation between the pressure drop and flow rate (c.f. Jaeger & Matthys, 1969 and references contained therein). By assuming a power law relation and calculating the power of the relation, they determined the flow regime; for example, if there was a linear relation between the pressure drop and flow rate, then the flow should be laminar (fully developed Poiseuille Flow). Jaeger & Matthys (1969) measured the pressure drop between the mouth and trachea and found that the power of the flow rate vs. pressure relation was approximately 1.55 ± 0.07 (mean $\pm$ standard error), which is between the values for fully developed laminar flow (1.0), and for fully developed turbulent flow (1.75).

One explanation for this result is that the flow is not fully developed. The relation between pressure drop and flow rate is only linear for fully developed laminar flow. The hydrodynamic entrance length, x_h , for a tube of diameter D is approximately

$$\frac{x_h}{D} \approx 0.05 \text{Re}_D \quad (2.8)$$

where Re_D is the Reynolds number based on the diameter of the tube. For flows typically seen in the extrathoracic region, the entrance length is on the order of 50 diameters, so laminar flow in the extrathoracic region would not exhibit a linear flow rate vs. pressure relation. The power of the relation between the flow rate and pressure drop may also be the result of secondary flows, or the onset of turbulence. These flow structures remove energy from the flows, and result in a greater power for the relation between flow rate and pressure drop.

From these results, we can conclude that turbulence is likely present in the flow inferior to (below) the larynx during normal tidal breathing. Superior to (above) the

larynx, the flow regime is not clear, but flows more complex than simple Poiseuille flow are expected.

In contrast with the extrathoracic region, the fluid mechanics of the lungs have been more extensively studied. Pedley (1977) reviews the research available at that time and concludes that the flow in the trachea and first few generations of the lungs can be expected to be turbulent. The depth to which the turbulence persists is unclear, but it is expected to decay quickly, as the Reynolds number drops to a few hundred after approximately 5 generations.

A rough estimate of how many generations through which the turbulence might persist can be found by considering the characteristics of the turbulence. As we are following a bolus of aerosol through the respiratory tract, the correct timescale for estimating the decay time is the Lagrangian timescale, T_L . By definition, the dissipation ϵ is equal to the time rate of change of the turbulence kinetic energy, i.e.:

$$\frac{1}{2} \frac{d}{dt} (q^2) = \frac{-q^2}{B_3 T_L} = \frac{3u_s^2}{B_3 T_L} = -\epsilon \quad (2.9)$$

where u_s is a velocity scale for the turbulent fluctuations. Snyder & Lumley (1971) found $B_3 \approx 5.0$, so using Equation (2.9) and the viscous limit definition of ϵ , we can write:

$$T_L = 0.3 \frac{\lambda^2}{\nu} \quad (2.10)$$

where λ is a correlation length of the turbulence. If we now assume that production P is approximately equal to the dissipation, we can write:

$$P \equiv u_s^2 \frac{U_s}{\delta} = \epsilon \equiv \frac{u_s^3}{l} = \frac{\nu u_s^2}{\lambda^2} \quad (2.11)$$

where U , is the mean flow velocity, and δ is the boundary layer thickness. Solving Equation (2.11) for λ^2 and subbing into Equation (2.10) with the boundary layer thickness equal to the radius of the airway, we get:

$$T_L = \frac{0.3 \left(\frac{wd}{2U} \right)}{\nu} = 0.15 \frac{d}{U} \quad (2.12)$$

If decay takes five timescales, and the residence time t for a turbulent eddy in a generation is $t = L/U$, then the decay time can be written:

$$\text{decay-time} = 0.75 \frac{d}{L} t \quad (2.13)$$

where d/L is the ratio of the diameter to the length of the generation, often on the order of 0.2 for the first few generations of a Weibel 'A' lung. Equation (2.13) shows us that the decay time for turbulence in a generation of the lung is a fraction of the residence time of the eddy in that generation. Therefore, we can expect that very little turbulence to be convected beyond the lung generation in which it is produced.

The depth to which turbulent flow can be expected in the lungs is therefore a question of to which depth the turbulence can be produced. In branching networks of tubes, turbulence can be produced at Reynolds numbers as low as 400 (Wilson, 1997). Depending on the inhalation flow rate, this level is reached in the first few generations of the lungs. Pedley (1977) suggests that turbulence is present in the flow in the 5th or 6th generation, which appears reasonable considering the turbulence scales.

Flow through central airway bifurcations has been extensively studied both experimentally (Schroter & Sudlow 1969, Olson *et al.* 1970, Olson 1972, Olson *et al.* 1973, Chang & Masry 1982, Isabey & Chang 1982) and computationally (Hofmann &

• Balàshàzy 1991, Balàshàzy & Hofmann 1993, Ferron & Eisner 1996). All authors show strong secondary flows, and asymmetric velocity profiles in the daughter tubes. The strength of the flows is found to be strongly dependent on the geometry of the bifurcation and the flow rate. The geometry usually used in these studies corresponds to the first few generations of the lung, yet rarely do the studies consider the effect of a turbulent inlet profile, or the effect of secondary flows from upstream bifurcations.

Acinar fluid mechanics are more difficult to study owing to the poorly characterized geometry of these structures, and because they change size and shape with lung inflation (Haefeli-Bleuer & Weibel, 1988) and straight rigid tubes are often assumed. Based on the Weibel 'A' model, the Reynolds number of the flow in the acini is of $O(1)$, and creeping flow (i.e. no inertial forces and strong viscous forces) can be expected. Recently, Tsuda *et al.* (1996) studied the fluid mechanics and aerosol deposition in a rhythmically expanding acinus using both numerical and experimental techniques. They found that despite the low Reynolds number, the flow is not reversible, and this may contribute to the observed dispersion of inhaled aerosol boluses (c.f. Heyder *et al.* 1988b).

Breathing is inherently an unsteady and transient activity. Unsteady effects on the flow in the respiratory tract were reviewed by Pedley (1977) and argued to be negligible for tidal breathing. In addition, Finlay *et al.* (1996a) conclude that transient effects may only be important near the start or end of exhalation. Here we accept these arguments, and assume that transient and unsteady effects are not important factors affecting particle deposition during tidal breathing.

2.4 Particle deposition mechanisms

2.4.1 Particle deposition in bifurcating systems of cylindrical tubes

In our deposition model, the lungs are modeled as a series of bifurcating cylindrical tubes. The probability of a particle depositing in a tube is dependent on the dimensions of the tube and the flow velocity of the carrier gas. In general, larger particles are deposited by inertial impaction and gravitational sedimentation, while smaller particles tend to be deposited by diffusion. In a dynamical deposition model, equations are written for each of the three deposition mechanisms, and the probabilities are then combined to give a deposition probability for a given particle in a given generation of the lung model. Particles may also deposit by interception and electrostatic precipitation. No distinction is made here between interception and impaction, and it has been argued (Lippmann, 1977) that electrostatic precipitation is not an important deposition mechanism for aqueous therapeutic aerosols. For the deposition of therapeutic aerosols in the human respiratory tract, the most important deposition mechanisms are impaction, which dominates in the extrathoracic region and in the first few bronchial airways, and sedimentation, which is the most important mechanism deeper in the lung.

2.4.1.1 Inertial Impaction

The path followed by air as it is inhaled through the mouth and branching airways of the lungs has many bends. Each time the air changes direction, particles entrained in the air tend to maintain their pre-established trajectories, and may impact on an airway wall. The probability of a particle depositing at a bend in the flow is a function of the

stopping distance for the particle, S , and a characteristic dimension of the flow, D . The ratio of these quantities is the Stokes number, Stk :

$$Stk = \frac{S}{D} = \frac{\rho d_{ae}^2 U}{18\mu D} \quad (2.14)$$

where ρ = particle density;
 d_{ae} = particle aerodynamic diameter;
 U = characteristic velocity of the flow;
 μ = dynamic viscosity of the carrier gas;
 D = a characteristic dimension of the flow.

Figure 2.4 shows how the Stokes number varies in a Weibel 'A' lung geometry scaled to 3000 cm³ for particles with diameters of 2.5, 5.0, and 10.0 μ m, at flow rates of 300 cm³/s and 500 cm³/s. It can be seen that the Stokes number is much higher in the bronchial airways (generations 1 to 16) than in the alveolar regions (generations 17-23), so we might expect that inertial impaction is most important in the bronchial airways. This conclusion is supported by *in vivo* deposition studies (e.g. Lippmann, 1977) where researchers found that tracheobronchial deposition with a wide range of particle diameters and flow rates could be described by a single function of the "impaction parameter", d^2Q , where Q is the inhalation flow rate. It follows from Equation 2.14 that the impaction parameter is directly proportional to the Stokes number.

Treatment of the deposition of particles by impaction in deposition models is not straightforward. Research in this area has been done with casts of the airways (e.g. Schlesinger *et al.* 1977, Chan & Lippmann 1980, Gurman *et al.* 1984), models of bifurcations (e.g. Johnston *et al.* 1977, Kim *et al.* 1994), and by theoretical analysis of the

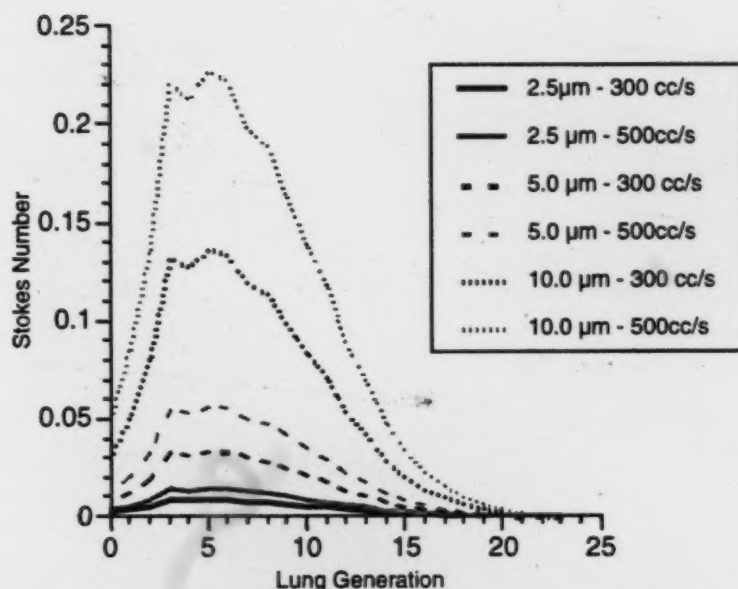


Figure 2.4. Plot of Stokes number (Equation 2.14) vs. lung generation for the scaled Weibel 'A' model lung for three particle sizes and two flow rates.

geometry and flow conditions (e.g. Gawronski & Szewczyk 1986, Cai & Yu 1988, Balàshàzy *et al.* 1991).

Schlesinger *et al.* (1977) present detailed results of the deposition of 2.5 - 8.1 μm particles in a six generation cast of the tracheobronchial airways including a trachea. The deposition probabilities they obtained in generations 1 and 2 were lower than those reported by Schlesinger & Lippmann (1972) who performed similar tests in a three generation cast without a trachea, suggesting that flow artifacts generated in the trachea decrease the deposition in the first two generations. Data on another cast with a trachea was collected by Chan & Lippmann (1980). They combined their data with that of Schlesinger *et al.* (1977) and obtained the following empirical equation to describe the

deposition due to impaction in any bifurcation based on the Stokes number of the parent airway (D = parent airway diameter, and U = parent airway air velocity):

$$\eta_{TB} = 1.606Stk + 0.0023 \quad (2.15)$$

Gurman *et al.* (1984) studied the deposition of 3 and 8 μm particles in casts of the bronchial airways with steady and cyclic flow and found that deposition with cyclic flow was significantly greater than with steady flow. However, Gurman *et al.* use a respiration frequency of approximately 40 breaths per minute, which is much higher than is seen in normal human breathing (ICRP, 1994). Thus, although their results may show that unsteady effects can affect the deposition of aerosol particles in airway bifurcations, the artificially high respiration frequency makes their results for cyclic flow of limited applicability for the inhalation of therapeutic aerosols during tidal breathing or forced inhalation maneuvers like those seen with patients using MDIs and DPIs. An equation based on an empirical fit to the data of Gurman *et al.* (1984) is used in the deposition model of the ICRP (1994).

Johnston *et al.* (1977) studied deposition in simple bends and bifurcating tubes. Experimentally, they found that both Stk and branching angle are important parameters characterizing deposition. Their results indicate that there is negligible deposition for $Stk < 0.1$, which is contrary to more recent experimental data in airway casts and from theoretical calculations, so their data is of limited use for deposition models.

Kim & Iglesias (1989), Kim *et al.* (1989), and Kim *et al.* (1994) studied experimental aerosol deposition in models of bifurcating airways. They found that the deposition probability depended mainly on the Stokes number in the parent tube, and slightly on the diameter ratio of the daughter and parent tubes. The bifurcation angle was

varied between 30 and 45 degrees, but did not have a significant effect on the results.

Likewise, both symmetrical and asymmetrical bifurcations gave similar results. They present two equations to predict the deposition probability in bifurcations:

$$\eta_{TB} = 3.7417Stk^{1.16} - 0.0394 \quad (2.16)$$

for a daughter to parent diameter ratio greater than 0.8, and:

$$\eta_{TB} = 1.5714Stk^{0.62} - 0.1299 \quad (2.17)$$

for a daughter to parent diameter ratio of 0.64, where both equations are valid for $Stk \cdot 0.02$.

As an alternative to experimental measurements, an equation for the deposition of particles by impaction can be obtained by considering the forces acting on particles flowing through bent tubes. Findeisen (1934) and Landahl (1950) present crude equations based on the impaction of aerosols in 90° bends. More recently, Gawronski & Szweczyk (1986) used the concept of stopping distance to derive equations for the inertial deposition of particles in bent tubes which show good agreement with experimental deposition data from lung casts and bifurcation models:

$$\eta = \frac{16}{3\pi} \phi \cdot Stk \left(2 - \sqrt{\frac{4}{3} \phi \cdot Stk} \right) \quad (2.18)$$

where

$$\phi = 2 \left(\frac{d}{d_0} \right)^2 \sin \alpha ;$$

α = bifurcation angle;

d = diameter of daughter branch;

d_0 = diameter of parent branch;

Stk = Stokes number of the daughter branch.

Cai & Yu (1988) found errors in this work, and rederived the equations while extending the theory to include the deposition of fibers. Their equations are a linear

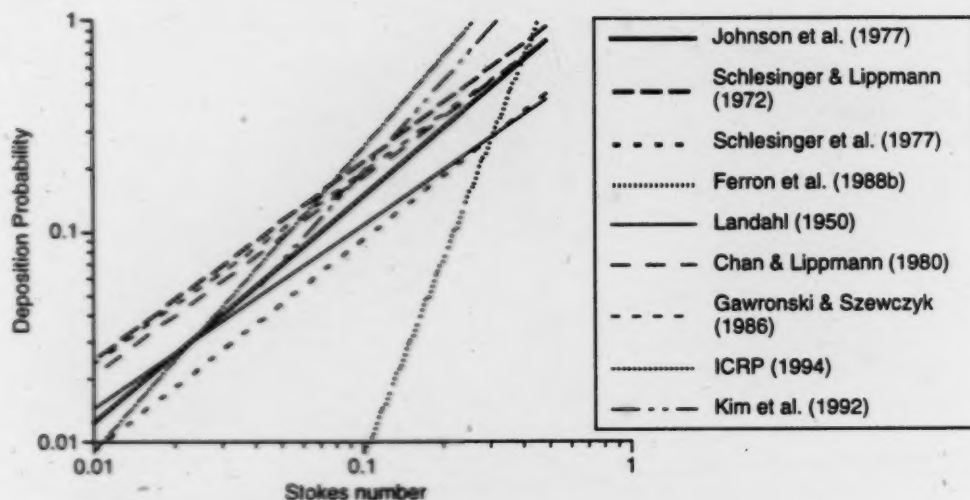


Figure 2.5. Common equations used to predict deposition due to impact in deposition models.

function of the Stokes number of the parent tube, and include corrections for branching angle and parent/daughter diameter ratio. Balàshazy *et al.* (1990) consider the forces acting on particles in bent tubes and present equations for deposition due to the combined action of inertial impaction and gravitational sedimentation in bent tubes and bifurcations with varying flow profiles. Their equations also predict the local deposition sites of the aerosol within the bifurcation, which agree well with the local deposition sites seen in the experimental results of Kim *et al.* (1989). The equations presented by both Cai & Yu (1988) and Balàshazy *et al.* (1990) compare well with the experimental data of Schlesinger *et al.* (1977) and Chan & Lippmann (1980) for the deposition of aerosols in airway casts.

Care must be taken when comparing the various equations used to estimate inertial impaction in bifurcating airways due to the different definitions of the Stokes number. Figure 2.5 plots many of the equations commonly used to predict aerosol

deposition in bifurcations for Stokes numbers for aerosol particles between 1 μm and 10 μm in the respiratory tract. It can be seen in Figure 2.5 that the equations all behave similarly. Particle deposition predictions in the model presented in this thesis use Equation (2.15) from Chan & Lippman (1980) to predict the deposition due to inertial impaction. This equation was chosen because it is based on the deposition seen in multi-generation airway casts, and therefore includes the effects of secondary flows not included in the theoretical equations and the single generation studies with bifurcation models

2.4.1.2 Sedimentation

The theory of aerosol deposition from fully developed laminar flow in horizontal tubes (Walton, 1954, Thomas, 1958, Fuchs, 1964, Pich, 1972) is well developed, and can be described by:

$$\eta_s = \frac{2}{\pi} \left[2\epsilon \sqrt{1 - \epsilon^{2/3}} - \epsilon^{1/3} \sqrt{1 - \epsilon^{2/3}} + \arcsin(\epsilon^{1/3}) \right] \quad (2.19)$$

where

$$\epsilon = \frac{3v_s L}{8rU} \equiv \text{sedimentation parameter;}$$

v_s = particle settling velocity;

L = length of tube;

U = average flow velocity;

r = tube radius.

Wang (1975) extended this theory to inclined tubes, and found different expressions for uphill and downhill flows. However, when the magnitude of the projection of the settling velocity of the particles in the direction of the fluid flow is small compared to the maximum velocity of the laminar flow, i.e.:

$$\frac{v_s}{u} \sin \beta \ll 1 \quad (2.20)$$

then the equations for both uphill and downhill flow can both be approximated by

Equation (2.19) with the sedimentation parameter defined by:

$$\epsilon = \frac{3v_s L}{8rU} \cos \beta \quad (2.21)$$

where β is the angle with respect to horizontal. Heyder & Gebhart (1977) experimentally validated Equations (2.19) and (2.21). Additionally, Heyder & Gebhart integrated Equations (2.19) and (2.21) through a network of randomly oriented tubes, and found that the deposition in the network differs by less than 2% from the deposition in a single tube inclined at $\beta=38.25^\circ$ from the horizontal for values of ϵ less than approximately 0.5, and by less than 10% for values of ϵ up to 1.0. Values of ϵ are typically less than 0.5 in the bronchial airways, so Equations (2.19) and (2.21) will give good predictions of the deposition probabilities due to sedimentation in the bronchial airways, but may underpredict the deposition probabilities by as much as 10% in the alveolar airways since values of ϵ in the range $0.5 \leq \epsilon \leq 1.0$ often occur in these airways.

As discussed previously, it is likely that the flow in the trachea and the first few generations of the lungs is turbulent, making the applicability of Equation (2.19) in this region suspect. Brockmann (1993) discusses sedimentation from turbulent pipe flow, and shows that for values of ϵ less than 0.5 (given by Equation 2.21), the deposition probability does not differ significantly from that seen in laminar flows. During tidal breathing, ϵ is less than 10^{-3} in the first few generations of the lungs for an aerosol with an MMD of 5.0 and GSD of 1.7, so the assumption of laminar flow in those regions will not affect the deposition predictions significantly. Additionally, it has been argued by

many of the researchers studying the impaction of aerosols in the bronchial airways, that the probability of a particle depositing by sedimentation in the first few generations of the bronchial airways is not significant compared to the probability of the particle depositing by impaction. For these reasons, we use Equation (2.19) for predicting deposition due to sedimentation throughout all lung airways

2.4.1.3 Diffusion

Diffusion is an important deposition mechanism for particles smaller than approximately 1 μm . Above that size it is normally negligible, but is included here for completeness, and for improving the deposition estimates of particles in the range of 0.5 μm to 1.0 μm .

Gormley & Kennedy (1949) developed an equation for the deposition of spherical particles from Poiseuille flow in tubes as a function of a diffusion parameter h :

$$h = \frac{Dt}{4r^2} \quad (2.22)$$

where:

D = diffusion constant;
 t = residence time in tube;
 r = radius of tube.

Gormley & Kennedy's derivation was confirmed by Ingram (1975) who added an extra term to the solution to give:

$$\eta_D = 1 - 0.819e^{-14.63h} - 0.0976e^{-89.22h} - 0.0325e^{-228h} - 0.0509e^{-125.9h^{2/3}} \quad (2.23)$$

to improve the predicted values of the deposition coefficient. Gormley & Kennedy give an asymptotic solution to their equation which is less than 1% different from Equation (2.23) for h less than approximately 0.1 (Ingram, 1975):

$$\eta_D = 6.41h^{2/3} - 4.8h - 1.123h^{4/3} \quad (2.24)$$

Cohen *et al.* (1990) measured the deposition of ultrafine particles with diameters between 0.04 μm and 0.2 μm in casts of the tracheobronchial airways and showed that Equation (2.23) underestimates the measured deposition probability, and theorize that this is the result of the equations not accounting for the secondary flows present in bifurcating airways. Yu & Cohen (1994) derive an expression that includes the effects of the secondary flows and predicts measured deposition probabilities for particles between 0.01 μm and 0.4 μm . The differences between the equation of Yu & Cohen (1994) and Equation (2.24) are less than 10^{-3} for particles larger than 0.5 μm . For an aerosol with an MMD of 5.0, and a GSD of 1.7, inhaled at 300 cm^3/s (which is typical for the aerosols considered here), values of the diffusion parameter h are less than 10^{-3} for more than 98% of the aerosol mass. We therefore use Equation (2.24) to estimate the deposition in the airways.

2.4.2 Extrathoracic deposition

As discussed previously, the geometry and fluid flow in the extrathoracic region of the respiratory tract is complex, and developing dynamical equations for predicting deposition probabilities in this region is difficult. For this reason, it is common to use empirical expressions to estimate the filtering efficiency of the mouth and throat. For mouth breathing, the filtering efficiency of the extrathoracic region can be approximated by (Rudolf *et al.* (1990):

$$\eta_{E, \text{Mouth}} = 1 - \left(1.10 \times 10^{-4} (d_{ae}^2 Q^{0.6} V_T^{-0.2})^{1.4} + 1 \right)^{-1} \quad (2.25)$$

where $\eta_{E, \text{Mouth}}$ = filtering efficiency of the region for mouth breathing;
 d_{ae} = aerodynamic particle diameter;
 Q = inhalation flow rate (cm^3/s);

V_T = tidal volume (cm³).

If a mask is used instead of a mouthpiece to conduct the aerosol from the nebulizer to the patient, then deposition in the nasal passages must be considered as well.

For the aerodynamic deposition of aerosol particles in the nose, Rudolf *et al.* (1990) give:

$$\eta_{E, Nose} = 1 - \left((2.05 \times 10^{-4} d_{ae}^2 Q) + 1 \right)^{-1} \quad (2.26)$$

where Q is the flow rate through the nasal passages.

2.5 Respiratory tract deposition models

2.5.1 Calculation of deposition probabilities

In a Lagrangian dynamical respiratory tract deposition model, the respiratory tract is viewed as a series of filters, where each generation of the lung model is a filter. Particles deposit in each generation due to the combined actions of inertial impaction, gravitational sedimentation, and Brownian diffusion. The geometrical model of the airways consists of the mouth, throat (the larynx and pharynx are both considered to be part of the throat), trachea, and the 23 generations of the Weibel 'A' model. To assist with the programming of the model, we use an 'extended Weibel' numbering system in which the nose and mouth are generation 1, the throat is generation 2, the trachea is generation 3, and the Weibel lung generations are labeled generations 4 through 26, with generations 3-19 corresponding to the bronchial region, and generations 20-26 corresponding to the alveolar region.

There are three phases to a normal tidal breathing cycle: inhalation, inspiratory pause, and exhalation. Inhalation is followed by the inspiratory pause, and the rest of the

breathing cycle is exhalation. For tidal breathing, the average breathing cycle is approximately 4 seconds long, with a 1.74 second inhalation, 0.2 second pause, and a 2.06 second exhalation (ICRP, 1994). For tidal volumes smaller than the size of the lung model, only L generations will be ventilated, where $L \leq 26$. The normal tidal volume for an adult Caucasian male is approximately 700 cm³, giving $L = 24$.

2.5.1.1 Deposition during inhalation

For combined nose and mouth breathing, the filtering efficiency of the nose is written:

$$\eta_1 = (1 - \psi)\eta_{E,nose} \quad (2.27)$$

where $\eta_{E,nose}$ is given by Equation (2.26), and ψ is the fraction of the aerosol inhaled through the mouth. Since mouth deposition is considered part of pharyngeal deposition, and for nasal breathing the effect of the dead space is negligible, the deposition in generation 1 is given by Equation (2.1) and can be written:

$$DE_1^{in} = \eta_1 \quad (2.28)$$

During pure mouth breathing, all particles are assumed to deposit at the end of the pharynx (i.e. in the larynx). The probability that a particle inhaled through the mouth or nose will deposit in the pharynx is then given by Equation (2.3), i.e.:

$$DE_2^{in} = (1 - \eta_1)\eta_{E,mouth}\phi_2 \quad (2.29)$$

where $\eta_{E,mouth}$ is given by Equation (2.25), and ϕ_2 is the fraction of the tidal volume that passes entirely through the pharynx and is equal to:

$$\phi_2 = 1 - (V_{mouth} + V_{pharynx}) = 1 - \sum_{k=1}^2 V_k \quad (2.30)$$

where V_k is the fraction of the tidal volume occupied by generation k . For an adult male during tidal breathing, $\phi_2 \approx 0.85$.

In the lungs, inertial impaction, gravitational sedimentation, and Brownian diffusion each contribute to the filtering efficiency of each generation. Assuming that each process acts independently, the total filtering efficiency for generation k can be written:

$$\eta_k^{in} = 1 - (1 - \eta_i)(1 - \eta_s)(1 - \eta_D) \quad (2.31)$$

where η_i is given by Equation (2.15), η_s is given by Equation (2.19), η_D is given by Equation (2.24), and the values of the parameters (e.g. tube radius, Stokes number) in Equations (2.15), (2.19), and (2.24) correspond to the values for generation k .

Using Equation (2.31), the fraction of the inhaled aerosol which deposits in generation k can then be written:

$$DE_k^{in} = \left(\prod_{i=0}^{k-1} (1 - \eta_i^{in}) \right) \cdot \phi_k \eta_k^{in} = f_k \phi_k \eta_k^{in} \quad (2.32)$$

where f_k is the fraction of the inhaled aerosol that penetrates to generation k , and ϕ_k is the fraction of the tidal volume that passes entirely through generation k , and is given by:

$$\phi_k = 1 - \sum_{i=1}^k V_i \quad (2.33)$$

2.5.1.2 Deposition during the inspiratory pause

The probability that a particle will deposit in generation k during the inspiratory pause is equal to the fraction of inhaled particles which are in the generation at the end of inspiration, multiplied by the probability that the particle will deposit during the pause.

During the inspiratory pause, there is no flow through the airways, and therefore no deposition due to inertial impaction. Equation (2.31) becomes:

$$\eta_k^{hold} = 1 - (1 - \eta_s)(1 - \eta_D) \quad (2.34)$$

and the probability that an inhaled particle with deposit in generation k during the inspiratory pause is:

$$DE_k^{hold} = f_k (1 - \eta_k^{in}) \eta_k^{hold} V_k = f_{k+1} \eta_k^{hold} V_k \quad (2.35)$$

2.5.1.3 Deposition during exhalation

Particles that are available for deposition during exhalation must not have deposited during inhalation or the inspiratory pause. Therefore, the deposition during exhalation can be written:

$$DE_k^{ex} = f_{k+2} V_{k+1} (1 - \eta_{k+1}^{hold}) \eta_k^{ex} + \sum_{i=k+2}^L f_{i+1} V_i (1 - \eta_i^{hold}) \prod_{j=k+1}^{i-1} (1 - \eta_j^{ex}) \eta_{kk}^{ex} \quad (2.36)$$

where η_k^{ex} is given by the RHS of Equation (2.31), the same equation as was used to calculate η_k^{in} , and L is the last ventilated generation. It is assumed that there is no deposition in the extrathoracic region during exhalation.

2.5.1.4 Total and Regional deposition

The total deposition is calculated from:

$$DE_E = DE_1^{in} + DE_1^{hold} + DE_2^{in} + DE_2^{hold} \quad (2.37)$$

The total deposition in a lung generation can be calculated by summing the deposition during inhalation, the inspiratory pause, and exhalation, i.e.:

$$DE_k = DE_k^{in} + DE_k^{hold} + DE_k^{ex} \quad (2.38)$$

Tracheo-bronchial deposition is then calculated from:

$$DE_{TB} = \sum_{k=3}^{19} DE_k \quad (2.39)$$

and alveolar deposition is calculated from:

$$DE_{Alv} = \sum_{k=19}^L DE_k \quad (2.40)$$

The total deposition in the respiratory tract is simply the sum of the regional depositions given by Equations (2.37), (2.39), and (2.40).

2.5.1.5 Polydisperse aerosols

Polydisperse aerosols are easily treated by discretizing the aerosol distribution into evenly spaced diameter subdivisions, or ranges. Many of the deposition equations reviewed in Section 2.4 depend on the square of the particle diameter, indicating that relatively small changes in particle size can have a large change in deposition probability. For this reason, diameter subdivisions less than or equal to 1 μm are used.

Once the distribution has been discretized, the diameter of each particle class is allowed to fluctuate independently of each other. Hence, there is no restriction on the shape of the particle size distribution.

2.5.2 Hygroscopic effects

Most therapeutic aerosols contain hygroscopic substances, usually in the form of organic or inorganic hydrophilic salts. This complicates the calculation of deposition probabilities, since the aerosol particles may grow or shrink as they travel through the respiratory tract. This can dramatically affect their fate since the diameter of a particle is an important parameter in the estimating its deposition probability (c.f. Morrow, 1986,

and Hiller, 1989 for reviews on this subject). Gebhart *et al.* (1990) studied the deposition of initially solid NaCl particles in the respiratory tract, and found that the measured deposition in the respiratory tract is similar to that of non-hygroscopic particles approximately 4 times the initial size of the NaCl particles.

Various authors have modified models for predicting the deposition of non-hygroscopic aerosols to account for the size changes common with hygroscopic aerosols (Persons *et al.* 1987, Ferron *et al.* 1988b, Stapleton *et al.* 1994, Finlay & Stapleton, 1995). These models calculate the growth and shrinkage of the droplets in response to their environment. Modifications are made to basic deposition equations so that the particle size used in the deposition equation for a specific generation of the airway is the average size of the particle in that generation.

Many hygroscopic models only calculate the size changes of hygroscopic particles in response to the environment of the respiratory tract and neglect the effect of the particles on the environment. These are referred to as one-way coupled models. The model described here also considers the effects of particle size changes on the environment of the respiratory tract, and is called a two-way coupled model. As will be shown later, two-way coupling is an important consideration for calculating the correct deposition of therapeutic aerosols produced by nebulizers.

2.5.2.1 Governing Equations

The equations governing the transfer of heat and water vapour between aerosol droplets and the continuous phase are discussed in detail by Fuchs (1959), Mason (1971), Heidenreich (1994) and are used in the context of lung deposition modeling by Ferron

(1977), Persons *et al.* (1987), and Ferron & Soderholm (1990), among others, and are reviewed here for completeness. Assuming a polydisperse aerosol discretized into N evenly spaced diameter ranges with n_i particles per unit volume in the i th size range with an average diameter d_i , the equation governing the diameter of the i th particle size can be written as:

$$\frac{dm_i}{dt} = 2\pi d_i D_w C_w (c_w - c_{oi}) \quad i = 1, \dots, N \quad (2.41)$$

where

- $m_i = \frac{\rho_i \pi d_i^3}{6}$ is the mass of a droplet of the i th size range with diameter d_i ;
- D_w = diffusion coefficient of water vapour in air;
- C_w = Knudsen correction (c.f. Ferron, 1977);
- c_w = water vapour concentration in the bulk continuous phase;
- c_{oi} = water vapour concentration at the surface of the droplet.

The density of the i th droplet is calculated from its initial solute and water content and its current size (c.f. Ferron, 1977), with mass changes due solely to the evaporation or condensation of water. The water vapour pressure reduction at the surface of the droplet due to dissolved NaCl is calculated with the empirical equation of Cintokai (1971) which includes non-linear changes in the dissociation constant with concentration. The vapour pressure reduction due to other dissolved components is calculated assuming dilute solutions (i.e. using Raoult's Law) and a constant van't Hoff factor. For many therapeutic aerosols based on normal saline, the contribution to the total vapour pressure reduction at the particle surface from components other than NaCl is negligible.

The equation governing the temperature of the i th particle size is:

$$m_i C_p \frac{dT_i}{dt} = Q_{ci} + Q_{mi} \quad i = 1, \dots, N \quad (2.42)$$

where C_{p_w} is the specific heat of water (and is assumed to be independent of temperature). Here, Q_m is the latent heat transfer, and Q_c is the conductive heat transfer.

These are given by:

$$Q_m = \frac{dm_i}{dt} L \quad (2.43)$$

$$Q_c = 2\pi d_i \kappa_a C_T (T_\infty - T_i) \quad (2.44)$$

where

- L = the latent heat of condensation;
- κ_a = the thermal conductivity of air;
- T_∞ = temperature of the continuous phase;
- T_i = temperature at the surface of the droplet.

The latent heat of condensation is negative and is assumed to be independent of temperature, while the thermal conductivity of air is assumed to vary linearly with temperature (Incropera and DeWitt, 1990). The Knudsen correction C_T in Equation (2.44) and C_m in Equation (2.41) account for noncontinuum effects and are discussed in detail elsewhere (e.g. Ferron & Soderholm, 1990), and their importance is discussed by Heidenreich & Büttner (1995).

The heat and mass transport from the droplets, given by Equations (2.41) - (2.44), is driven by the difference in temperature and water vapour concentration between the continuous phase, and the surface of the droplet. Heat and mass transferred to the continuous phase from the discrete phase changes the temperature and relative humidity of the continuous phase, which affects the heat and mass transfer rate. This coupling of the heat and mass transfer rates between the discrete and continuous phases requires that the water vapour concentration, c_w , and temperature, T_∞ , are calculated simultaneously with the particle size as the bolus moves through the respiratory tract.

The equation governing the water vapour concentration as the bolus carrying the droplets moves through the respiratory tract can be written as:

$$\frac{dc_w}{dt} = \dot{m}'_{wall} - \sum_{i=1}^N n_i \frac{dm_i}{dt} \quad (2.45)$$

The second term on the right-hand side of Equation (2.45) accounts for the mass transfer occurring at the droplet surfaces, and is obtained from a simple mass balance. The first term on the right-hand side of Equation (2.45), $\dot{m}'_{wall}$, accounts for the mass transfer from the airway walls to the continuous phase. This term can be evaluated using a mass transfer coefficient, g'_k , (Kays & Crawford, 1980) for each generation k in the lung, so that the mass transfer rate in the k th generation is:

$$\dot{m}'_{wall} = g'_k (c_{wall} - c_w) \quad (2.46)$$

The value of the mass transfer coefficient, g'_k , can be calculated from the known temperature and humidity profiles of the respiratory tract when no droplets are present in the inhaled air (Ferron *et al.*, 1988a, Daviskas *et al.*, 1990) from:

$$g'_k = \frac{(\Delta c_w^0)_k}{\Delta t_k (\bar{c}_{wall} - \bar{c}_w^0)_k} \quad (2.47)$$

where $(\Delta c_w^0)_k$ is the change in water vapour concentration between the beginning and end of the k th generation when no droplets are present, and $(\bar{c}_{wall} - \bar{c}_w^0)_k$ is the difference between the average water vapour concentration of the continuous phase in the k th generation and the average value at the airway walls when no droplets are present. The value of Δt_k in Equation (2.47) is the amount of time a bolus of air spends in the k th generation when traveling at the bulk flow velocity in that generation. Within each

generation, the mass transfer coefficient g'_k is assumed to be independent of mass transfer rate, implying an assumption of relatively low mass transfer rate (Kays & Crawford, 1980).

Similarly, the equation governing the temperature of the continuous phase as the bolus moves through the respiratory tract can be written:

$$(c_{-}C_{p_{-}} - \rho_{-}C_{p_{-}}) \frac{dT_{-}}{dt} = \dot{q}'_{wall} - \sum_{i=1}^N n_i Q_i \quad (2.48)$$

where $C_{p_{-}}$ is the specific heat of air (and is assumed to be independent of temperature), and ρ_{-} is the density of air. As in Equation (2.45), the second term on the right-hand side of Equation (2.48) accounts for the heat transfer to the continuous phase due to conduction from the discrete phase, and the first term on the right-hand side of Equation (2.48), $\dot{q}'_{wall}$, accounts for the heat transfer from the airway walls, and can be written:

$$\dot{q}'_{wall} = h'_k (T_{wall} - T_{-}) \quad (2.49)$$

where the heat transfer coefficient h'_k in the k th generation is evaluated in a manner similar to the mass transfer coefficient g'_k given in Equation (2.47) using the known temperature profiles in the lung when no droplets are present (Daviskas *et al.* 1990), and can be written:

$$h'_k = \frac{[(\bar{\rho}_{-}^0)_k C_{p_{-}} + (\bar{c}_{-}^0)_k C_{p_{-}}] (\Delta T_{-}^0)_k}{\Delta t_k (\bar{T}_{wall} - \bar{T}_{-}^0)_k} \quad (2.50)$$

where

$(\bar{\rho}_{-}^0)_k$ = average density of air in the k th generation;

$(\bar{c}_{-}^0)_k$ = average water vapour concentration of the continuous phase in the k th generation;

$(\Delta T_{-}^0)_k$ = temperature change in the continuous phase between the proximal

and distal ends of the k th generation;
 $(\bar{T}_{wall} - \bar{T}_{\infty}^0)_k$ = difference between the average wall temperature and temperature
of the continuous phase in the k th generation.

All of the quantities in Equation (2.50) are evaluated when no droplets are present in the inhaled air.

It is common practice in Lagrangian dynamical models to neglect momentum boundary layers and assume a plug flow velocity profile within the airways. Since the Prandtl and Schmidt numbers are both of $O(1)$ in the continuous phase, it is then consistent to also neglect thermal and mass diffusion boundary layers. With this assumption, the aerosol bolus will remain as a continuous plug as it travels through the respiratory tract, and the heat and mass transferred per unit volume to the continuous phase from the airway walls in each lung generation are then the average amounts transferred per unit volume of flow through the generation.

Equations (2.41) - (2.50) represent a set of $2N+2$ coupled, nonlinear, ordinary differential equations that govern $2N+2$ unknowns associated with the diameters and temperatures of N droplet sizes, and the temperature and water vapour concentration of the continuous phase. These equations must be solved numerically. In addition, the number of droplets in the bolus is an important parameter in determining the water vapour concentration and temperature of the continuous phase from Equations (2.45) and (2.48), requiring Equations (2.41) - (2.50) to be solved simultaneously with the deposition equations.

2.5.2.2 Solution methodology

At the beginning of each generation, the coefficients g'_k and h'_k are calculated for the generation. An aerosol bolus is then tracked through the generation and their sizes calculated by solving Equations. (2.41) - (2.50) using the SFODE routine of the Naval Surface Warfare Center for numerical analysis library (Morris, 1993, Finlay & Stapleton, 1995). An average size for each particle size range is then calculated for the generation, and is used to calculate deposition probabilities for each particle size range using the equations described in Section 2.5.1. The number of particles per unit volume of the bolus is reduced by multiplication of the number densities with the calculated deposition probabilities so that particles deposited in this generation do not contribute to the heat and mass transport between the discrete and continuous phases in subsequent generations. This process is repeated for all generations of the lungs ventilated during the breathing.

The SFODE routine uses a variable order backward differentiation (BDF) method with adaptive, variable size time step. The BDF method is an implicit method, and therefore requires the solution of a $(2N + 2) \times (2N + 2)$ set of linear equations for each time step. For a typical therapeutic aerosol with an MMD = 5.0, and a GSD = 1.7, $N = 20$ is common, and this causes computation times to be approximately 100 times greater than those seen for non-hygroscopic aerosols.

2.5.2.3 One-way Coupling

In one way coupling, heat and mass transfer between the discrete and continuous phases does not affect the temperature or water vapour concentration of the continuous phase. This assumption is valid for aerosols with low number concentrations where the

water vapour and heat exchanged between the phases is negligible compared to the amount contained in the continuous phase. This assumption uncouples the $2N$ equations associated with Equation (2.41) and Equation (2.42), and the equations for each particle size can be solved independently of each other.

The model described in this thesis has the option of using one-way coupling to calculate the growth of hygroscopic particles. If this option is selected, the model is similar to that of Ferron *et al.* (1988b), although the temperature and water vapour concentration of the continuous phase is given by the model of Daviskas *et al.* (1990), and the vapour pressure reduction at the surface of the droplets due to dissolved NaCl is given by the empirical equation of Cintokai (1971). (Additionally, there are differences in the deposition equations for the extrathoracic region and deposition due to impaction in the airways.)

The main advantage of one-way coupling is that it greatly reduces the computational time required to calculate the size of the aerosol particles as they move through the respiratory tract. For the aerosol considered in Section 2.5.2.2 where $N = 20$, computation times are only approximately 5 times greater than those seen for non-hygroscopic aerosols, or 1/20 of those seen using two-way coupling.

Finlay & Stapleton (1995) show that for the aerosols typically produced by nebulizers, a one-way coupled model underpredicts the dosage delivered to the extrathoracic region by as much as 137%, with total and bronchial dosages in error by as much as 10%, and alveolar dosages in error by as much as 20% (see Section 3 of this thesis for a description of the methodology to calculate the dosage delivered to the regions of the lungs). Consequently, two-way coupling is preferred unless it can be

demonstrated that the number densities of the aerosol are low enough that one-way coupling can be used without incurring significant error.

2.5.2.4 Hygroscopic vs. Nonhygroscopic calculations

While it is accepted that most therapeutic aerosols are hygroscopic, it is not clear whether hygroscopic effects are an important consideration when estimating their deposition in the respiratory tract. Clark (1995) found that the relative distribution between the upper and lower airways determined *in vivo* with planar gamma scintigraphy is adequately modeled when hygroscopic effects are neglected, suggesting that the added complexity and cost of including hygroscopic effects in deposition models is unnecessary.

A possible explanation for Clark's observation is that the heat and mass transferred between the discrete and continuous phases may reduce the importance of hygroscopic size changes (Finlay *et al.* 1997c). Finlay *et al.* calculate the dosage delivered to the extrathoracic, bronchial, and alveolar regions of the respiratory tract for a variety of common jet nebulizers using three different hygroscopic models (i.e. non-hygroscopic, one-way and two-way coupled). They found that when the ambient relative humidity (RH) of the testing laboratory was 90%, hygroscopic effects are unimportant, since all three methods of treating hygroscopic effects gave similar results. At an ambient relative humidity of 50%, they found that significant errors in the estimates of the delivered dosages are seen for nebulizers that output low number density aerosols when assuming stable particles, or one-way coupling. At an ambient relative humidity of

15%, they found that two-way coupling was an important consideration for non-vented nebulizers.

The above data suggests that a non-hygroscopic deposition model may give adequate estimates of the deposition from some nebulizers, but because the coupled heat and mass transfer effects depend on many factors, including ambient relative humidity, properties of the inhaled aerosol, and the breathing pattern of the individual, it is not possible to make a general statement that hygroscopic effects are not important for nebulized aerosols (Finlay & Stapleton, 1996a, Finlay *et al.* 1997c). Therefore, caution must be exercised if a coupled hygroscopic model is not used when modeling the deposition of nebulized aerosols.

2.5.3 Intersubject variability

The Lagrangian dynamical deposition model described in this thesis uses an "average" lung geometry, and therefore predicts the deposition for an "average" person, as do all other deposition models using idealized lung geometries (e.g. Martonen *et al.* 1982, Persons *et al.* 1987, Xu & Yu 1985, Ferron *et al.* 1988b, among others). However, experimental data of aerosol deposition in the human respiratory tract shows that there are significant differences in deposition probabilities between one person and another (cf. Goldberg & Lourenço 1973, Stuart 1973, Lippmann 1977, Lippmann *et al.* 1980, Stahlhofen *et al.* 1989, Morrow & Yu 1993, and references contained therein) and the resulting variation in deposition probabilities is not accounted for in most deposition models. The main causes of intersubject variability in total lung deposition are unclear. Morrow & Yu (1993) argued that the main cause of the intersubject variability is

differences in lung morphology between individuals, and to a lesser extent, differences in breathing pattern. Heyder *et al.* (1982) and Heyder *et al.* (1988a) came to similar conclusions by comparing the deposition in subjects who were breathing spontaneously and with a controlled breathing pattern. However, Bennett (1988) reviewed the available literature and concluded that breathing pattern variability in humans is greater than variability in peripheral airspace size, and therefore breathing pattern played a more important role in the observed intersubject variability.

Because one of the main causes of intersubject variability is differences in lung morphology between individuals, Yu and Diu (1982a) consider using different lung geometries with a single deposition model as a possible way of estimating intersubject variability. They showed reasonable agreement with experimental data, and found that calculations performed with a Weibel 'A' lung geometry approximate the population average. However, this method has the disadvantage of requiring several times the computing time of a single lung geometry. Run times of tens of hours are seen on high-performance workstations (IBM RS6000 Model 59H) when dosage estimates are obtained for a nebulizer using the model described in this thesis with two-way coupled heat and mass transfer between the droplets and the surrounding continuous in a single lung geometry. Therefore, using multiple lung geometries is not a practical solution for estimating the intersubject variability in a reasonable number of delivery devices.

Yu and Diu (1982b) present a probabilistic model for predicting intersubject variability in regional deposition probabilities that agrees well with the experimental data of Stahlhofen (1981). However, this method requires a numerical integration of the deposition model over different lung volumes, which also requires multiple runs of the

deposition model, and is again currently impractical for use with two-way coupled, hygroscopic deposition models.

The empirical stable particle deposition model of Rudolf *et al.* (1990) includes equations for the 95% confidence intervals for extrathoracic, fast- and slow-cleared thoracic deposition. The equations are based on data from different labs and reflect different breathing patterns (i.e. controlled vs. spontaneous), and measurement techniques. It has been shown (Heyder *et al.*, 1978) that different measurement techniques can report different deposition in the same populations, so the intersubject variability reflected in the equations for the confidence intervals may over-estimate the true value. However, it may still be possible to estimate the variability in regional dosages from the spread seen in experimental results. Gebhart *et al.* (1990) summarizes the experimental data on the total deposition of hygroscopic aerosols, but to the authors' knowledge, there is no data on the regional deposition of hygroscopic aerosols. There are, however, a significant number of studies on the regional deposition of stable particles, and it may be possible to adapt these results to a hygroscopic deposition model to estimate intersubject variability.

2.5.3.1 Calculation of intersubject variability

To estimate the intersubject variability in the calculations, experimental data on the deposition of non-hygroscopic monodisperse aerosols in the respiratory tract is considered (Lippmann & Albert 1969, Foord *et al.* 1978, Chan & Lippmann 1980, Lourenço *et al.* 1971, Emmett *et al.* 1982). By convention, we assume that fast-clearance corresponds to tracheo-bronchial deposition, and slow-clearance corresponds to

alveolar, even though there is some uncertainty in making these assumptions (c.f. section 2.6 of this thesis). Stahlhofen *et al.* (1989) summarize the experimental data for the regional deposition of non-hygroscopic aerosols, and note that some of the differences in the deposition measured at different labs are caused by different controls on the breathing parameters: studies where both the tidal volume and flow rate were controlled showed less intersubject variability than those where the patient breathed spontaneously (or only the number of breaths per minute was controlled). For our purposes, we are interested in predicting the variability in the dosage delivered from an aerosol therapy device during tidal breathing, and wish to include the variability resulting from spontaneous breathing as well as morphological differences. We therefore only consider data from experiments where the inhalation flow rate and tidal volume are not controlled.

For studies satisfying this criterion, the standard deviation of the deposition probability among the individual subjects participating in each monodisperse experiment is calculated, and normalized by the mean value. Figures 2.6, 2.7, and 2.8 show the normalized standard deviation for the regional deposition plotted against aerodynamic particle diameter. A third order polynomial is fit to the data with a least squares method (Table 2.2 gives the coefficients). The deposition model calculates an average deposition probability, P_n , for the aerosol particle in each generation n of an extended Weibel 'A' model. Using the average size of the aerosol particle in each generation, a value of the normalized standard deviation, $\sigma_{n, norm}$, is calculated from the fitted curves, and the standard deviation of the deposition probability, σ_n , is calculated from:

$$\sigma_n = P_n \times \sigma_{n, norm} \quad (2.51)$$

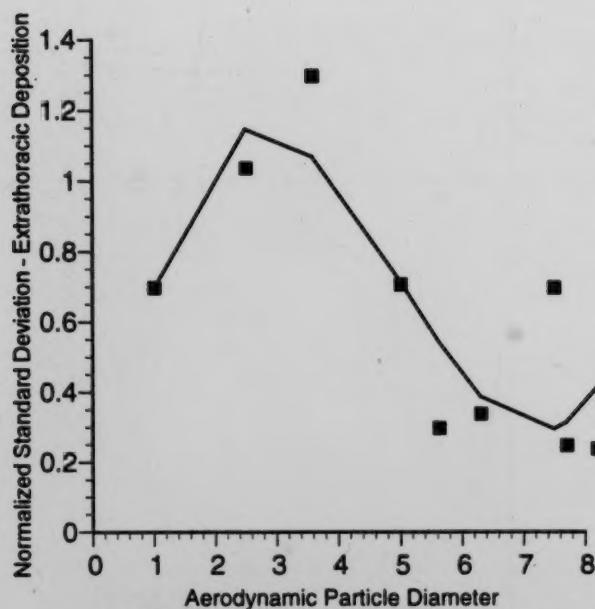


Figure 2.6. Normalized standard deviation vs. particle size for the extrathoracic region showing the 3rd order polynomial fit used in the model. Data from Lippmann & Albert (1969), and Foord *et al.* (1978).

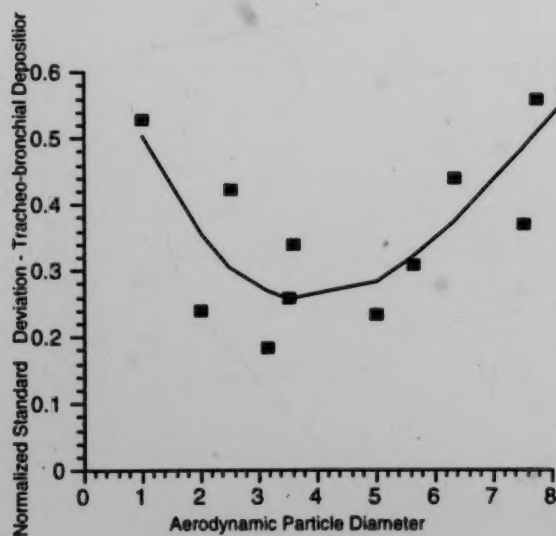


Figure 2.7. Normalized standard deviation vs. particle size for the tracheo-bronchial region showing the 3rd order polynomial fit used in the model. Data from Lippmann & Albert (1969), Chan & Lippmann (1980), Foord *et al.* (1978), Emmett *et al.* (1982), and Lourenço *et al.* (1971).

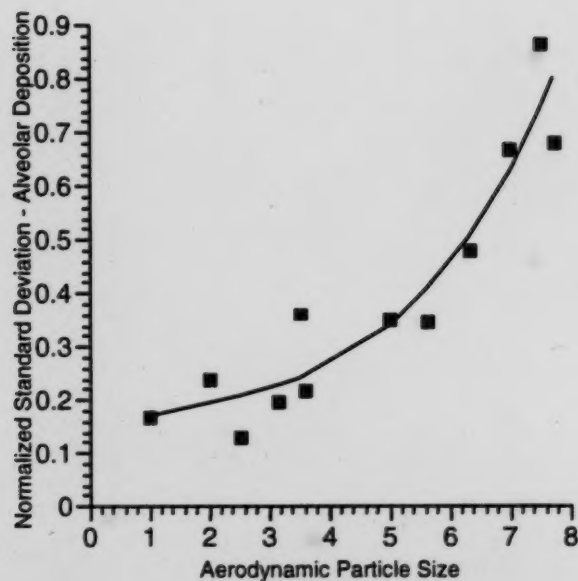


Figure 2.8. Normalized standard deviation vs. particle size for the alveolar region showing the 3rd order polynomial fit used in the model. Data from Lippmann & Albert (1969), Chan & Lippmann (1980), Foord *et al.* (1978), Emmett *et al.* (1982), and Lourenço *et al.* (1971).

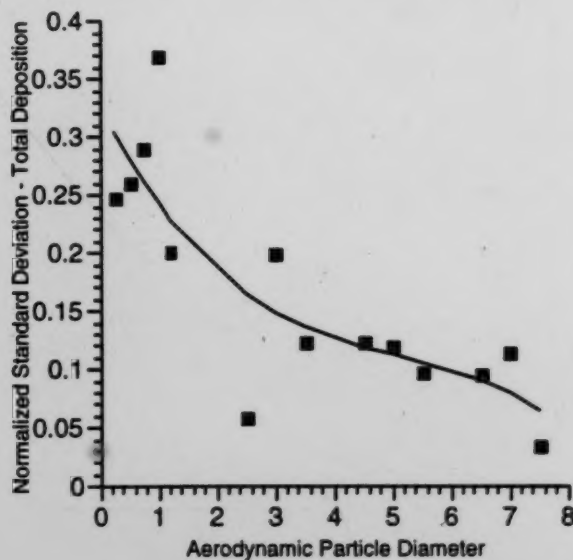


Figure 2.9. Normalized standard deviation vs. particle size for total deposition in the respiratory tract showing the 3rd order polynomial fit used in the model. Data from Lippmann & Albert (1969), Chan & Lippmann (1980), and Foord *et al.* (1978).

	a	b	c	d
Total deposition	-0.0012	0.0176	-0.1022	0.3279
Extrathoracic deposition	0.0183	-0.2739	1.0812	-0.1299
Tracheo-bronchial deposition	-0.0019	0.0470	-0.2771	0.7362
Alveolar deposition	0.0023	-0.0125	0.0468	0.1350

Table 2.2. Values of the coefficients for the 3rd order polynomial fits to the normalized standard deviation vs. particle size data, where $\sigma_{n,norm} = a * d_n^3 + b * d_n^2 + c * d_n + d$

The upper, $P_{n,upper}$, and lower, $P_{n,lower}$, values of the 68% confidence interval for the average deposition probability in each generation are calculated by standard statistical methods:

$$P_{n,upper} = P_n + \sigma_n \quad (2.52)$$

$$P_{n,lower} = P_n - \sigma_n \quad (2.53)$$

To assist in the verification of the procedure with available hygroscopic deposition data, the variation of the total deposition is required. To accomplish this, the procedure just described is used with experimental data on the total deposition of stable particles reported by Heyder *et al.* (1982), Giacomelli-Maltoni *et al.* (1972), Foord *et al.* (1978), and Lippmann *et al.* (1980). The variation of the normalized standard deviation with aerodynamic particle diameter is shown in Figure 2.9 along with the 3rd order polynomial fit. The coefficients for the fitted curve are given in Table 2.2.

2.6 Comparison with experimental data

The total and regional deposition of stable particles in the human respiratory tract *in vivo* has been well studied and reviewed in the archival literature (c.f. Goldberg & Lourenço 1973, Stuart 1973, Lippmann 1977, Lippmann *et al.* 1980, Stahlhofen *et al.* 1989, Morrow & Yu 1993, and references contained therein). Monodisperse aerosols labelled with a gamma ray emitter (typically technecium) are inhaled, and the lungs are imaged with a gamma camera.

Unfortunately, the deposition of hygroscopic aerosols has not been as extensively studied. A few measurements of the absolute total deposition of initially solid NaCl particles is available (Gebhart *et al.*, 1990), and deposition studies show a similar shape to that seen with solid particles if the deposition probabilities are plotted against equilibrium size of the particles (as opposed to the initially inhaled size). Additionally, some data is available for hygroscopic aerosols on the relative deposition between the central and peripheral regions of the lungs (e.g. Chan *et al.* 1994).

The regional distribution (or regional deposition) of aerosols in the lung is often studied by measuring the retention and clearance of aerosols from the respiratory tract. If it is assumed that aerosol deposited in the ciliated tracheo-bronchial airways are removed over a period of a few hours, then aerosol remaining in the lung over longer periods of time should be equivalent to alveolar deposition (Lippmann *et al.* 1980). By comparing gamma camera images over a number of hours, estimates of the tracheo-bronchial and alveolar deposition may be calculated.

There is some uncertainty in the assumption that fast-cleared aerosol is equivalent to bronchial deposition, and slow-cleared aerosol is equivalent to alveolar deposition

(ICRP, 1994). Inhalation studies with humans using aerosol boluses of solid particles and shallow breathing to control the deposition site in the airways have shown that a substantial fraction of the particles deposited in the bronchial airways may be cleared much slower than the conventionally assumed half-time of a few hours (Stahlhofen *et al.* 1987), and that the fraction of aerosol cleared after 24 hours decreases with decreasing particle size (Heyder *et al.* 1988b). Smaldone *et al.* (1988) suggests that solid aerosol particles depositing in the bronchial airways can be transported through the mucous layer, indicating that clearance times for particles in the ciliated bronchial airways can be on the same order as clearance times from the alveolar regions. Gehr *et al.* (1990) and Gehr *et al.* (1996) study this effect theoretically and experimentally, and show that latex particles can be pulled into the mucus layer toward the epithelium by interfacial forces.

This effect has not been proven to occur for the many different types of particles used in inhalation studies, so there may still be value in comparing the results of deposition models against clearance studies. Further validation of our model is given in Section 2.6.2 where we compare against experimental data on the deposition of hygroscopic aqueous aerosols, where the above mentioned uncertainties in interpreting clearance are not important.

2.6.1 Regional Deposition of Stable Aerosols

Figures 2.12, 2.13, and 2.14 show experimental data on the regional deposition of stable aerosols in the respiratory tract, along with the mean deposition probability predicted by our model, and our calculated 68% confidence interval. Breathing parameters used in the model calculations correspond to quiet breathing (tidal volume =

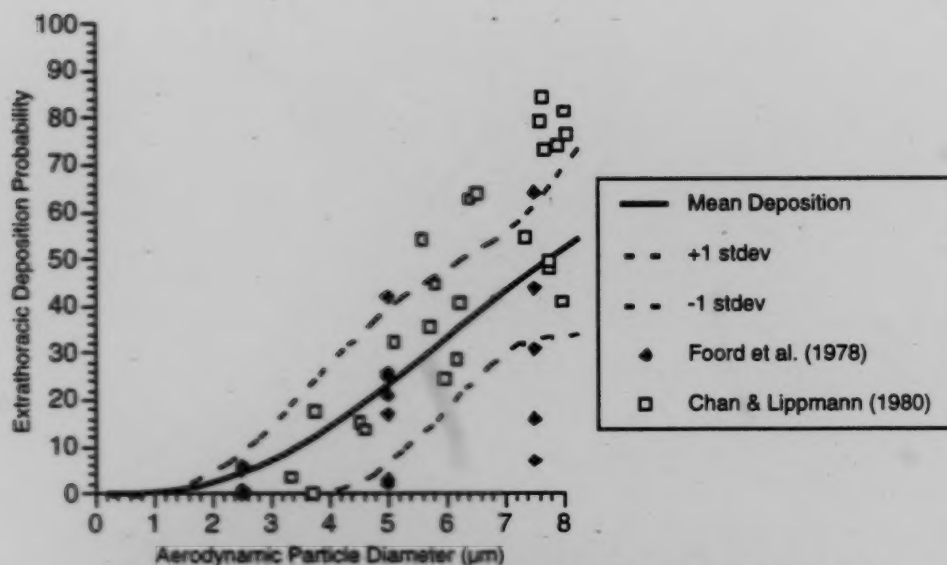


Figure 2.10: Experimental data on the deposition of stable particles in the extrathoracic region of the respiratory tract and the mean deposition and 68% confidence interval predicted by the model for a flow rate of 400 cm³/s and a tidal volume of 0.7 litres.

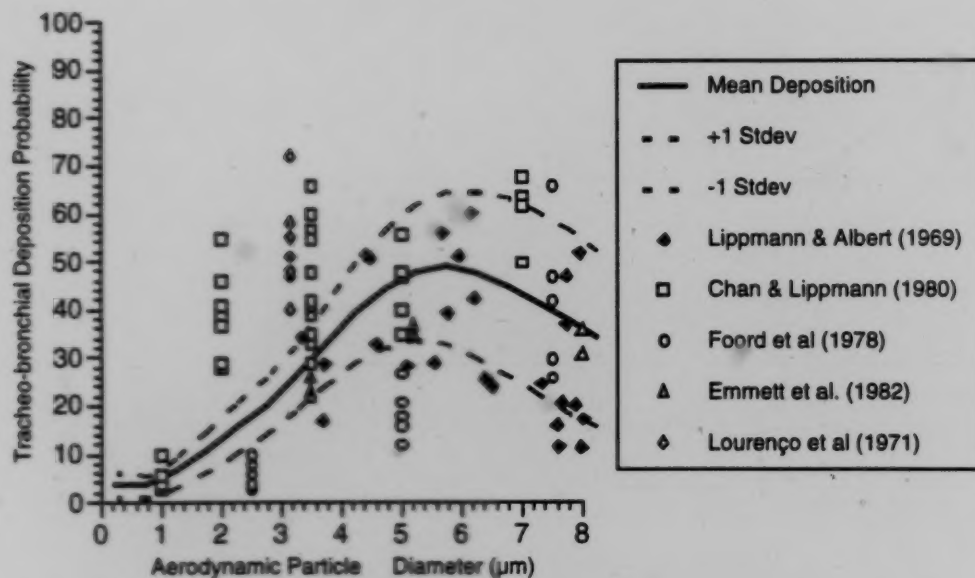


Figure 2.11. Experimental data on the deposition of stable particles in the tracheo-bronchial region of the respiratory tract and the mean deposition and 68% confidence interval predicted by the model for a flow rate of 400 cm³/s and a tidal volume of 0.7 litres.

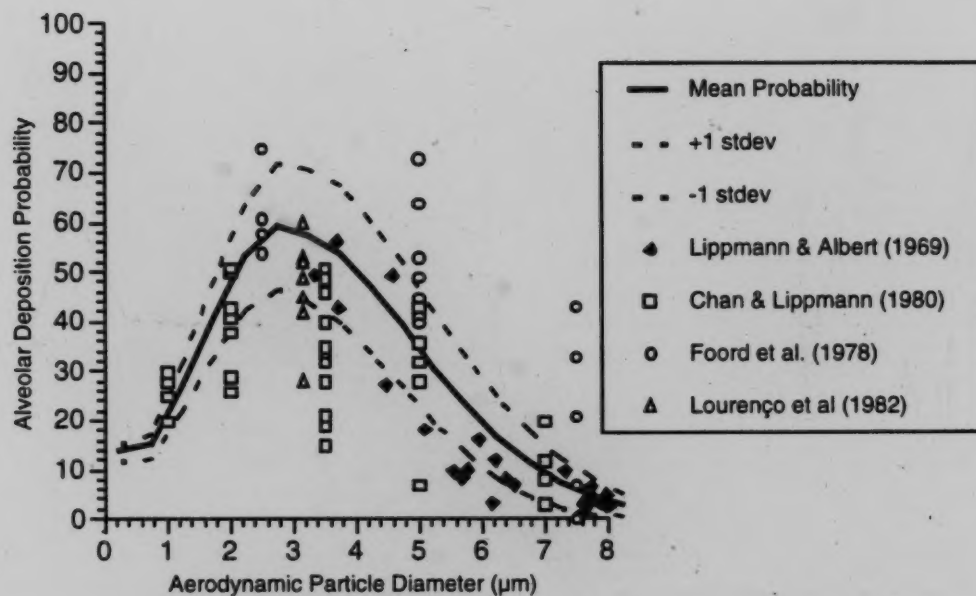


Figure 2.12. Experimental data on the deposition of stable particles in the alveolar region of the respiratory tract and the mean deposition and 68% confidence interval predicted by the model for a flow rate of 400 cm³/s and a tidal volume of 0.7 litres.

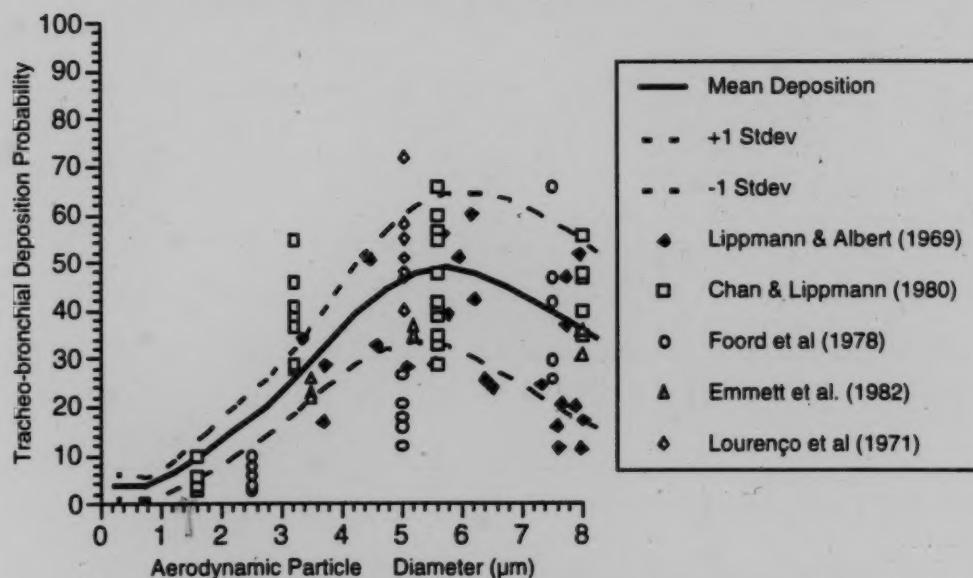


Figure 2.13. Experimental data on the deposition of stable particles in the tracheo-bronchial region of the respiratory tract and the mean deposition and 68% confidence interval predicted by the model for a flow rate of 400 cm³/s and a tidal volume of 0.7 litres. Iron oxide particles are corrected for hygroscopic growth.

700 cm³, inhalation flow rate 400 cm³/s, 4.0 second breathing cycle with a 1.74 second inhalation, 0.2 second breath hold).

In general, agreement between the model calculations and experimental data is good. In the extrathoracic region, 60% of the data points fall within the 68% confidence interval predicted by the model. In the alveolar region, 62% of the data points fall into the 68% confidence interval.

In the tracheo-bronchial region, 47% of the data points fall within the 68% confidence interval. The main cause of this disagreement is the lower mean deposition probability calculated by the model for particles between 2µm and 4µm compared to the experimental values. One possible explanation for this discrepancy is the mild hygroscopicity of iron oxide particles used in some of the studies. Gebhart *et al.* (1989) found that 2.4 µm iron oxide particles had a deposition probability similar to 3.8 µm oil droplets, suggesting approximately a 60% increase in the particle diameter as the iron oxide particles travel through the respiratory tract (ICRP, 1994). Figure 2.13 shows the same data as Figure 2.11, but with the size of the particles used in the iron oxide studies increased by 60%. The agreement with the experimental data is better, with 66% of the data points falling within the predicted 68% confidence interval. Note that the 7µm droplets from Chan & Lippmann (1980) shown in Figure 2.11 are not shown in Figure 2.13, and are not included in the above statistics.

Due to the relative scarcity of experimental data for the regional deposition of aerosols in the respiratory tract, most deposition models are validated against the same experimental data for nonhygroscopic aerosols shown here, and all show reasonable

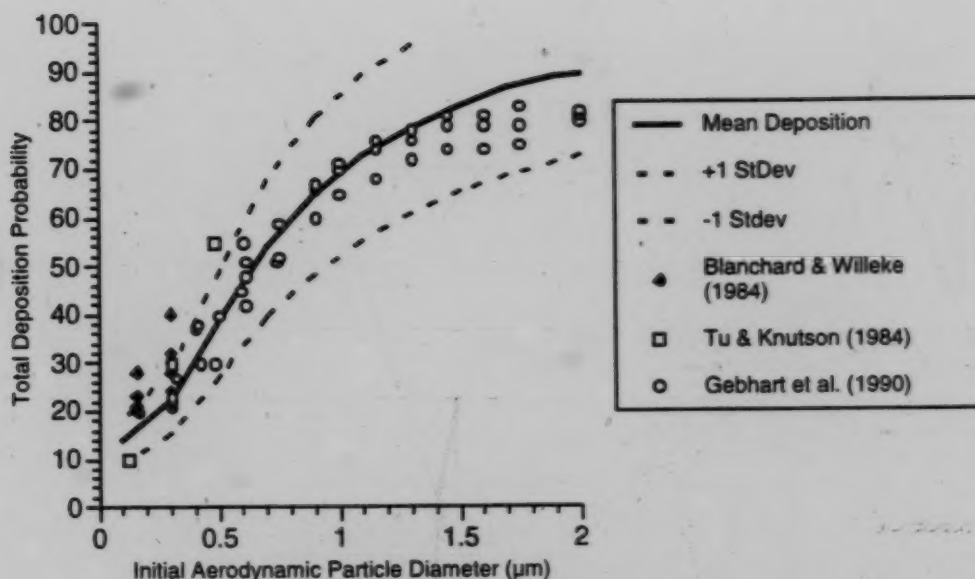


Figure 2.14. Experimental data on the total deposition of initially solid hygroscopic NaCl particles and the mean deposition and 68% confidence interval predicted by the model for a flow rate of 500 cm³/s and a tidal volume of 1.0 litres.

agreement with this data. We therefore do not include direct comparisons of the results of this model with the results of other models.

2.6.2 Total and Regional Deposition of Hygroscopic Aerosols

Gebhart *et al.* (1990) summarize the available experimental data on the total deposition of initially solid hygroscopic aerosols. Figure 2.14 shows this data plotted with the mean deposition probability predicted by the model, along with our calculated 68% confidence interval, for the breathing patterns used in the studies (all studies used a tidal volume of 1000 cm³ and an inhalation flow rate of 500 cm³/s). The mean deposition and variability predicted by the model agrees well with the experimental data, given the small number of subjects in the experiments. It should be noted that the inhalation flow

rate and tidal volume were controlled in the study of Gebhart *et al.* (1990) which may decrease their observed intersubject variability.

To the author's knowledge, there is no published experimental data on the absolute regional deposition of hygroscopic aerosols. However, data on the relative distribution of central to peripheral deposition for hygroscopic aerosols is available (Phipps *et al.* 1989, Phipps *et al.* 1994, and Chan *et al.* 1994). Finlay *et al.* (1996c) compared this experimental data to the predictions of the deposition model presented here and showed that there was no significant difference ($P > 0.05$) between the deposition measurements *in vivo*, and the results of this model. A complete description of the study is beyond the scope of this thesis, and the reader is referred to Finlay *et al.* (1996c) for details. However, a brief overview of the results is presented here for completeness.

In the experimental studies, the penetration index (PI) is defined as the ratio of the counts per pixel in the peripheral region divided by the counts per pixel in the central region. Therefore, the higher the penetration index, the more aerosol which deposits in the peripheral region. A 'd-value' is then defined to compare the penetration indexes of two aerosols such that (Phipps *et al.* 1989):

$$d = \frac{PI_1 - PI_2}{PI_1} \times 100 \quad (2.54)$$

where PI_1 and PI_2 are the penetration indexes of the two aerosols. In the study of Phipps *et al.* (1989), two aerosols of isotonic saline (MMAD 2.6 μm , GSD 1.4 vs. MMAD 5.5 μm , GSD 1.7) were compared. The d-value of the experimental study was 53.7 ± 12.3 (all values in this section are mean $\pm$ standard deviation) and the value predicted by the deposition model was 54.2 ± 10.8 . The next study, by Phipps *et al.* (1994) studied the

deposition of two aerosols with similar size distributions, but with different solution concentrations (MMAD 3.8 μm , GSD 1.4, 0.3% NaCl, vs. MMAD 3.7 μm , GSD 1.4, 4.5% NaCl). Here, the d-value in the experimental study was 4.0 ± 10.5 , and the value predicted by the deposition model was 6.8 ± 10.8 . In the study of Chan *et al.* (1994), the number densities of the droplets were reduced (MMAD 3.8 μm , GSD 1.4, 0.3% NaCl, vs. MMAD 3.7 μm , GSD 1.4, 4.5% NaCl) to enhance the effects of the hygroscopic growth. The experimentally determined d-value was 5.6 ± 10.6 , and the d-value predicted by the deposition model was 10.9 ± 15.4 . Again, no difference ($P > 0.05$) was found between the *in vivo* and computational results for either the mean value or the variance of the difference in peripheral to central deposition.

3. Regional Dosage Predictions from Medical Nebulizers

3.1 Introduction

As discussed earlier, our goal is to develop *in vitro* methods for evaluating the ability of different therapeutic aerosol delivery devices to deliver drugs to the respiratory tract. Deposition models such as those described in the previous section of this manuscript provide a way of estimating the regional deposition probabilities of inhaled aerosols, but cannot be used directly with therapeutic aerosol devices without considerable attention to a number of aspects. The purpose of Section 3 of this manuscript is to describe these aspects and the work we have done in order to use a deposition model to estimate regional dosages delivered to the respiratory tract by medical nebulizers.

It is useful to begin by considering what kinds of aerosols are produced by medical nebulizers, and what information will be required to calculate the regional deposition probabilities. For use in a nebulizer, drugs are usually formulated as an

aqueous solution (i.e. the drug is dissolved in water) or as a suspension (i.e. the drug is milled or dried into small particles and suspended in the water). In addition to the drug, the solution may contain NaCl and other salts in order that the tonicity and pH of the produced aerosol is similar to that of the airway surface fluid lining the respiratory tract. Surfactants and preservatives may also be present.

The aerosols produced by nebulizers will therefore be aqueous droplets, usually approximately lognormally distributed with a mass median diameter of between 3 and 9 μm , and a geometric standard deviation between 1.5 and 2.0. Nebulized aerosols can be expected to change size in response to changes in the temperature and relative humidity of their environment. This has two important implications. First, if the relative humidity of air entering the nebulizer is less than the equilibrium relative humidity of the droplets (see discussion of equation (3.7)), then the droplets will humidify the air in the nebulizer. The solution concentration within the droplets and nebulizer reservoir may then be different, and both will change with time. Second, a deposition model which accounts for the hygroscopic nature of the droplets will be required to correctly predict where they will deposit in the respiratory tract.

To use a hygroscopic deposition model to predict the deposition of a nebulized aerosol in the respiratory tract, the droplet size distribution, solution concentration in each droplet, and the droplet number density of the aerosol are required at the entrance to the respiratory tract. In the remainder of this chapter we discuss a methodology for determining these quantities. In short, the droplet size distribution is readily measured using, for example, phase Doppler anemometry. This measurement can be used to determine an estimate of the number density by considering a mass balance in the

nebulizer (see Section 3.3.1 for a detailed description). The solution concentration in the droplets cannot be readily measured directly, and requires additional considerations.

3.2 Nebulizer Types

There are three main types of nebulizers available today: unvented jet nebulizers, vented jet nebulizers, and ultrasonic nebulizers. Each type of nebulizer requires a different measurement approach, and it is useful to first review the performance features of each nebulizer type.

The simplest of the three nebulizer types is the unvented jet nebulizer, shown schematically in Figure 3.1. High pressure air (from a compressor, for example) enters through the bottom of the nebulizer, and is forced through a venturi (4). As the speed of the fluid increases through the venturi, the pressure decreases, and liquid is drawn into the airstream from the reservoir, forming the droplets. To exit the nebulizer, the aerosol passes through baffles (5) which allow only a certain size range of droplets to escape. Droplets outside this size range impact on the sides of the nebulizer and are returned to the reservoir in the bowl of the nebulizer (3) for renebulization. Droplets formed at the venturi are called primary droplets, and it has been estimated that over 99% of the primary droplets are returned to the reservoir for renebulization (Mercer *et al.* 1968, Smye *et al.* 1991).

Jet nebulizers are typically driven at compressor flow rates of approximately 6 liters/min, much lower than typical resting inhalation flow rates (for which 18 liters/min, or 300 cm³/s is a typical value). A T-mouthpiece (2) is used to mix in ambient air to make up the patient's inhalation flow rate.

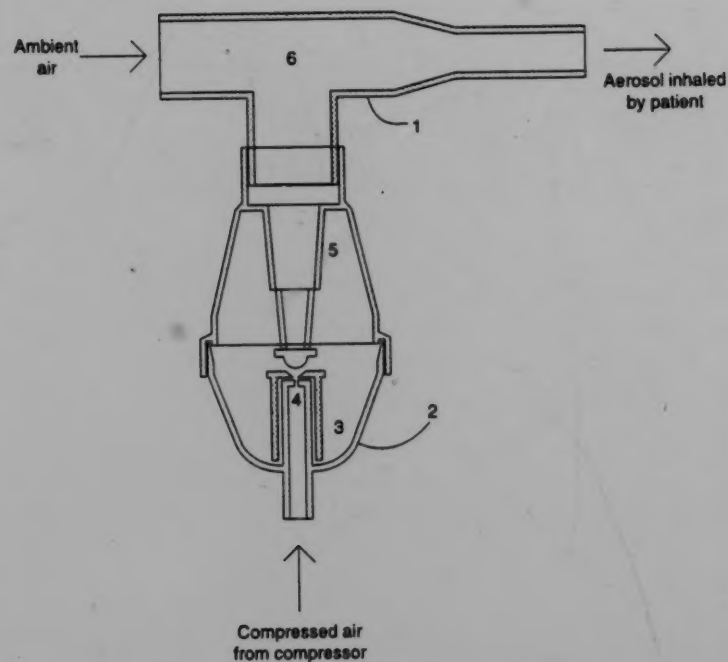


Figure 3.1. A schematic of an unvented jet nebulizer (2) with attached T-mouthpiece (1). The nebulizer has a reservoir (3), a venturi (4), and baffles (5). The aerosol produced by the nebulizer is mixed with ambient air at (6), which is also the point that the droplet size distribution is measured by the PDA system.

An important performance feature of unvented jet nebulizers is that ambient air entrained to make up the patient's inhalation flow rate does not travel through the droplet production region of the nebulizer. Therefore, the aerosol that exits the nebulizer (prior to mixing with ambient air at the junction of the T-mouthpiece) is independent of patient breathing.

Some jet nebulizers contain a vent in the body of the nebulizer to allow ambient air to pass through the nebulizer body. Here, these nebulizers are termed vented jet nebulizers, and a typical such nebulizer is shown schematically in Figure 3.2. The main

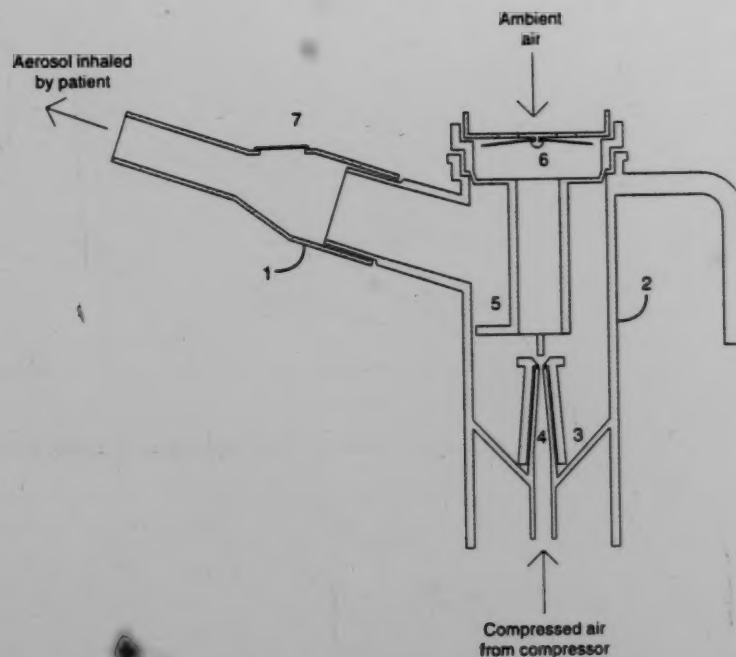


Figure 3.2. A schematic of a vented jet nebulizer (2) and attached mouthpiece (1) shown during inhalation. The nebulizer includes the reservoir (3), venturi (4) and baffles (5). When the patient inhales, air is drawn through the open inlet valve (6). During exhalation, the inlet valve (6) closes, and air is expelled through the exhalation valve (7).

difference between unvented and vented jet nebulizers is the air is drawn through the bowl of vented nebulizers during patient inhalation, in contrast to unvented jet nebulizers where ambient air needed to make up the patient's inhalation flow rate is drawn only through the mouthpiece.

It is important to note that during inhalation, the flow rate of air exiting the nebulizer mouthpiece is equal to the inhalation flow rate of the patient, which can vary in time. For many vented jet nebulizers, the mass flow rate of liquid leaving the nebulizer increases as the inhalation flow rate increases. For this reason, vented jet nebulizers are sometimes termed "breath enhanced" nebulizers. Depending on the design of the vented nebulizer, the number density of the aerosol (i.e. the number of droplets per cm^3) may